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Color Atlas of Pharmacology

Fifth Edition

Heinz Luellmann
Klaus Mohr
Lutz Hein

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Color Atlas of Pharmacology

Fifth Edition

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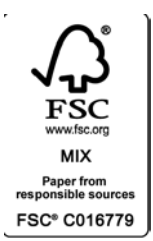

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Preface

In the European Union, about 25 new chemical preparations are approved annually for distribution as pharmaceutical products, approximately 10 of which are "innovative" drugs with a novel molecular mechanism of action. "New" is not always "better," thus new drugs undergo evaluation of their beneficial effects to establish whether new substances reflect an actual therapeutic improvement compared to existing structures, therefore justifying a possible increase in costs to the collective of insured persons.

The innovative strength of pharmaceutical manufacturers, licensing procedures, and the assessment of benefits, together form the basis for successful drug treatment, but the decisive factor is ultimately ensuring that individual patients have access to optimal "customized" treatment. This "therapeutic art" requires that pharmacological principles be understood, and not just memorized.

The *Color Atlas of Pharmacology* is intended to provide students of medicine, dental medicine, and pharmaceutics, as well as anyone with an interest in pharmaceuticals, with an overview of all the available information on pharmacological structures and their methods of action. Special emphasis is placed upon providing the information necessary to enable the reader to understand the principles of pharmacology. Purely factual information, for example, on dosages, can easily be found with an internet search. However, in order to make sense of the facts, connections are explained in graphics, mechanisms of action are clearly depicted, and new drug substances are listed together with existing ones. Many plates and text passages have been fundamentally revised in this new edition, and three completely new double-page spreads have been added. Modern specialized medications such as antibodies that fight malignant diseases and harmful infections, as well as kinase inhibitors, have been integrated into tabular overviews.

The concept of Luellmann's *Color Atlas of Pharmacology* recently celebrated its 25th anniversary. The Atlas was founded by Professor Heinz Luellmann in cooperation with Albrecht Ziegler, Klaus Mohr, and Juergen Wirth. Professor Luellmann passed away shortly before work on this new English edition was started. This edition is dedicated posthumously to his memory.

Klaus Mohr
Lutz Hein
Juergen Wirth

Disclosure: The authors of the *Color Atlas of Pharmacology* have no financial interests or other relationships that would influence the content of this book.

General Pharmacology

History of Pharmacology

Since time immemorial, medicaments have been used for treating disease in humans and animals. The herbals of antiquity describe the therapeutic powers of certain plants and minerals. Belief in the curative powers of plants and certain substances rested exclusively upon traditional knowledge, that is, empirical information not subjected to critical examination.

The Idea

Claudius Galen (AD 129–200) first attempted to consider the theoretical background of pharmacology. Both theory and practical experience were to contribute equally to the rational use of medicines through interpretation of the observed and the experienced results:

"The empiricists say that all is found by experience. We, however, maintain that it is found in part by experience, in part by theory. Neither experience nor theory alone is apt to discover all."

The Impetus

Theophrastus von Hohenheim (1493–1541), called Paracelsus, began to question doctrines handed down from antiquity, demanding knowledge of the active ingredients in prescribed remedies, while rejecting the irrational concoctions and mixtures of medieval medicine. He prescribed chemically defined substances with such success that professional enemies had him prosecuted as a poisoner. Against such accusations, he defended himself with the thesis that has become an axiom of pharmacology:

"If you want to explain any poison properly, what then is not a poison? All things are poison, nothing is without poison; the dose alone causes a thing not to be poison."

Early Beginnings

Johann Jakob Wepfer (1620–1695) was the first to verify by animal experimentation assertions about pharmacological or toxicological actions.

"I pondered at length. Finally I resolved to clarify the matter by experiments."

Foundation

Rudolf Buchheim (1820–1879) founded the first institute of pharmacology at the University of Dorpat (Tartu), Estonia in 1847, ushering in pharmacology as an independent scientific discipline. In addition to a description of effects, he strove to explain the chemical properties of drugs.

"The science of medicines is a theoretical, i.e., explanatory, one. It is to provide us with knowledge by which our judgment about the utility of medicines can be validated at the bedside."

Consolidation—General Recognition

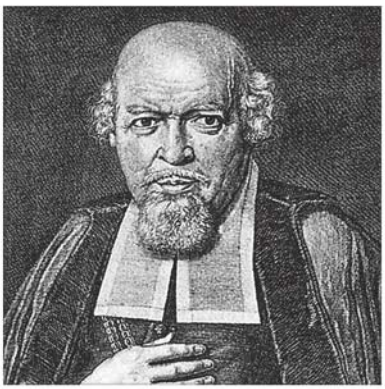
Oswald Schmiedeberg (1838–1921), together with his many disciples (12 of whom were appointed to chairs of pharmacology), helped to establish the high reputation of pharmacology. Fundamental concepts such as structure–activity relationships, drug receptors, and selective toxicity emerged from the work of, respectively, T. Frazer (1840–1920) in Scotland, J. Langley (1852–1925) in England, and P. Ehrlich (1854–1915) in Germany. Alexander J. Clarke (1885–1941) in England first formalized receptor theory in the early 1920s by applying the Law of Mass Action to drug–receptor interactions. Together with the internist Bernhard Naunyn (1839–1925), Schmiedeberg founded the first journal of pharmacology, which has been published since without interruption. The "Father of American Pharmacology," John J. Abel (1857–1938) was among the first Americans to train in Schmiedeberg's laboratory and was founder of the *Journal of Pharmacology and Experimental Therapeutics* (published from 1909 until the present).

Status Quo

After 1920, pharmacological laboratories sprang up in the pharmaceutical industry outside established university institutes. After 1960, departments of clinical pharmacology were set up at many universities and in industry.

Important figures in the history of pharmacology

◄ The idea: Claudius Galen (129–200)



▲ Theophrastus von Hohenheim, known as Paracelsus (1493–1541)

◄ Johann Jakob Wepfer (1620–1695)

▲ Rudolf Buchheim (1820–1879)

◄ Oswald Schmiedeberg (1838–1921)

Fig. 1.1

Drug and Active Principle

Until the end of the 19th century, medicines were natural organic or inorganic products, mostly dried, but also fresh, plants or plant parts. These might contain substances possessing healing (therapeutic) properties, or substances exerting a toxic effect.

In order to secure a supply of medically useful products not merely at the time of harvest but all year round, plants were preserved by drying or soaking them in vegetable oils or alcohol. Drying the plant, vegetable, or animal product yielded a drug (from French "drogue" = dried herb). Colloquially, this term nowadays often refers to chemical substances with high potential for physical dependence and abuse. Used scientifically, this term implies nothing about the quality of action, if any. In its original, wider sense, *drug* could refer equally well to the dried leaves of peppermint, dried lime blossoms, dried flowers and leaves of the female cannabis plant (hashish, marijuana), or the dried milky exudate obtained by slashing the unripe seed capsules of *Papaver somniferum* (raw opium).

Soaking plants or plant parts in alcohol (ethanol) creates a *tincture*. In this process, pharmacologically active constituents of the plant are extracted by the alcohol. Tinctures do not contain the complete spectrum of substances that exist in the plant or crude drug, but only those that are soluble in alcohol. In the case of opium tincture, these ingredients are alkaloids (i.e., basic substances of plant origin) including morphine, codeine, narcotine = noscapine, papaverine, narceine, and others.

Using a natural product or extract to treat a disease thus usually entails the administration of a number of substances possibly possessing very different activities. Moreover, the dose of an individual constituent contained within a given amount of the natural product is subject to large variations, depending upon the product's geographical origin (biotope), time of harvesting, or conditions and length of storage. For the same reasons, the relative proportions of individual constituents may vary considerably. Starting with the extraction of morphine from opium in 1804 by F.W. Sertürner (1783–1841), the active principles of many other natural products were subsequently isolated in chemically pure form by pharmaceutical laboratories.

The Aims of Isolating Active Principles

1. Identification of the active ingredient(s).
2. Analysis of the biological effects (pharmacodynamics) of individual ingredients and of their fate in the body (pharmacokinetics).
3. Ensuring a precise and constant dosage in the therapeutic use of chemically pure constituents.
4. The possibility of chemical synthesis, which would afford independence from limited natural supplies and create conditions for the analysis of structure–activity relationships.

Finally, derivatives of the original constituent may be synthesized in an effort to optimize pharmacological properties. Thus, derivatives of the original constituent with improved therapeutic usefulness may be developed.

Modification of the chemical structure of natural substances has frequently led to pharmaceuticals with enhanced potency. An illustrative example is fentanyl, which acts like morphine but requires a dose 10 to 20 times less than that of the parent substance. Derivatives of fentanyl such as carfentanyl (employed in veterinary anesthesia of large animals) are actually 5000 times more potent than morphine.

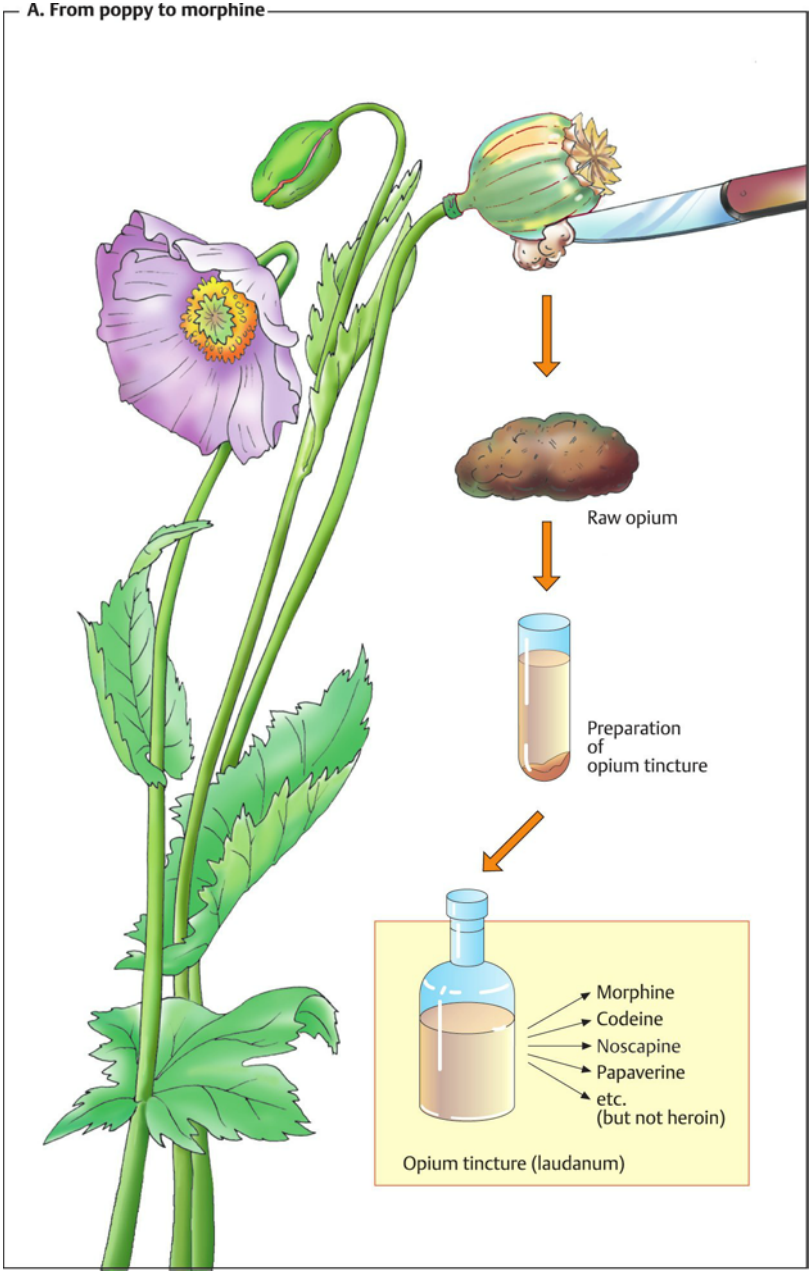

A. From poppy to morphine
Raw opium
Preparation
of
opium tincture
Morphine
Codeine
Noscapine
Papaverine
etc.
(but not heroin)
Opium tincture (laudanum)

Fig. 2.1

Plants as Sources of Effective Medicines

Since prehistoric times, humans have attempted to alleviate ailments or injuries with the aid of plant parts or herbal preparations. Ancient civilizations have recorded various prescriptions of this kind. In the herbal formularies of medieval times numerous plants were promoted as remedies. In modern medicine, where each drug is required to satisfy objective criteria of efficacy, few of the hundreds of reputedly curative plant species have survived as drugs with documented effectiveness. Presented below are some examples from local old-world floras that were already used in prescientific times and that contain substances that to this day are employed as important drugs.

a) A group of local plants used since the middle ages to treat "dropsy" comprises foxglove (digitalis sp.), lily of the valley *(Convallaria majalis)*, Christmas rose *(Helleborus niger)*, and spindletree *(Euonymus europaeus)*. At the end of the 18th century the Scottish physician William Withering introduced **digitalis leaves** as a tea into the treatment of "cardiac dropsy" (edema of congestive heart failure) and described the result. The active principles in these plants are steroids with one or more sugar molecules attached at C3 (see p. 148). Proven clinically to be the most useful among all available cardiac glycosides, **digoxin** continues to be obtained from the plants *Digitalis purpurea* or *D. lanata* because its chemical synthesis is too difficult and expensive.

b) The **deadly nightshade** of Central Europe *(Atropa belladonna,* a solanaceous herb)[1] contains the alkaloids **atropine**, in all its parts, and **scopolamine**, in smaller amounts. The effects of this drug were already known in antiquity; e.g., pupillary dilation resulting from the cosmetic use of extracts as eye drops to enhance female attractiveness. In the 19th century, the alkaloids were isolated, their structures elucidated, and their specific mechanism of action recognized. Atropine is the prototype of a competitive antagonist at the acetylcholine receptor of the muscarinic type (cf. p. 124).

c) The **common white willow** and **basket willow** *(Salix alba, S. viminalis)* contain salicylic acid derivatives in their bark. Preparations of willow bark have been used since antiquity; in the 19th century, **salicylic acid** was isolated as the active principle of this folk remedy. This simple acid still enjoys use as an external agent (keratolytic action) but is no longer taken orally for the treatment of pain, fever, and inflammatory reactions. Acetylation of salicylic acid (introduced around 1900) to yield **acetylsalicylic acid** (ASA, Aspirin®) improved oral tolerability.

d) The **autumn crocus** *(Colchicum autumnale)* belongs to the lily family and flowers on meadows in late summer and fall; leaves and fruit capsules appear in the following spring. All parts of the plant contain the alkaloid **colchicine**. This substance inhibits the polymerization of tubulin to microtubules, which are responsible for intracellular movement processes. Thus, under the influence of colchicine, macrophages and neutrophils lose their capacity for intracellular transport of cell organelles. This action underlies the beneficial effect during an acute attack of gout (cf. p. 350). Furthermore, colchicine prevents mitosis, causing an arrest in metaphase (spindle poison).

[1] This name reflects the poisonous property of the plant: Atropos was the one of the three Fates (moirai) who cut the thread of life.

A. Plants as sources of drugs

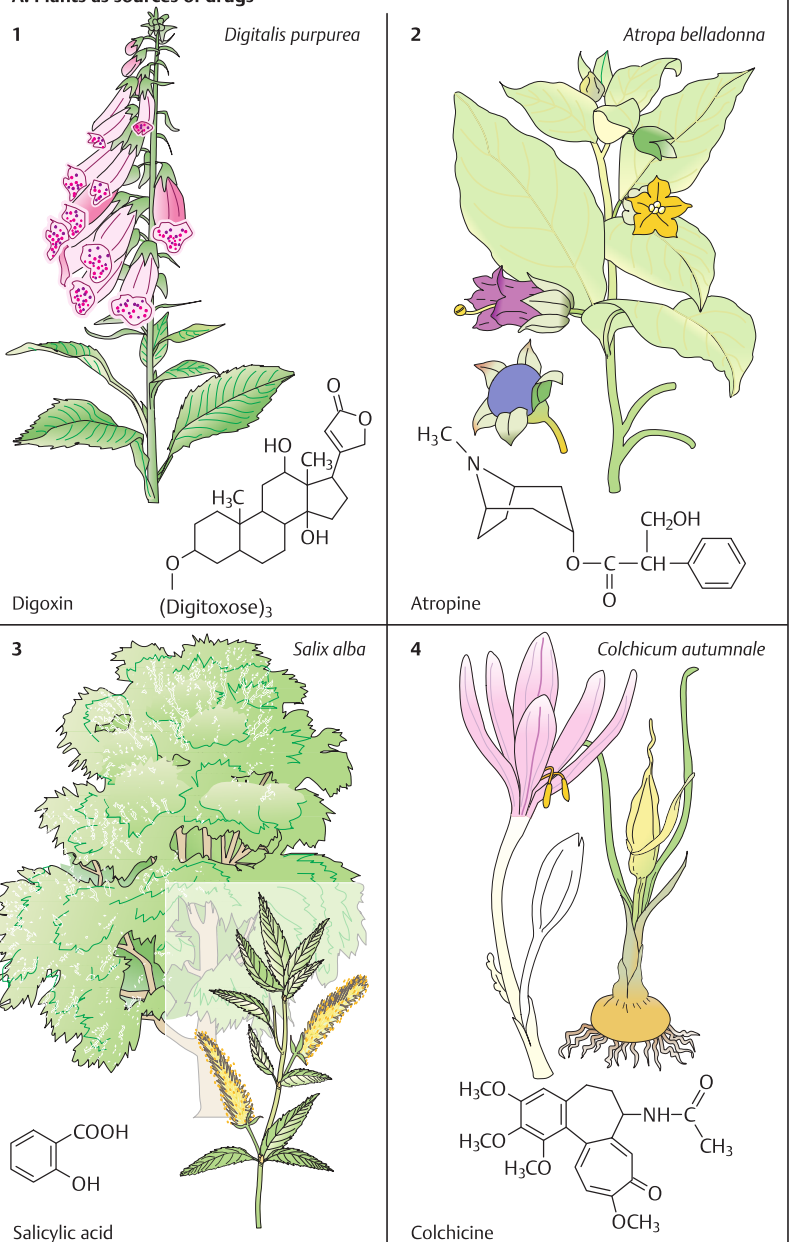


Fig. 2.2

Human Proteins as Medicines

Proteins that are used as medicines should match the "human template" so as to avoid immune-mediated intolerability reactions. Producing human proteins by means of classic organic chemistry synthesis would be very complex: whereas only 20 atoms have to be joined correctly to form the low-molecular-weight analgesic acetaminophen (paracetamol), an antibody involves roughly 25 000 atoms.

Genetic Engineering

The protein-coding cDNA is integrated in an expression plasmid and this is inserted into suitable host cells (▶ Fig. 2.3**A**). The chosen *cellular expression system* and *cell culture conditions* have a major influence on the product.

- *Mammalian cells* such as CHO (Chinese hamster ovary) cells can link carbohydrate residues to proteins; *bacteria* such as E. coli are unsuitable for production of *glycoproteins* but do allow production of nonglycosylated proteins.
- The *spatial (3D) structure* of the product depends in part on whether disulfide bridges occur and if so, which ones.
- The *amino acid sequence* and *charge* can be altered by subsequent deamidation of the amino acids asparagine and glutamine to aspartate and glutamate.

Meticulous attention to every detail of the production process and sophisticated analytical tests are needed to ensure that the product's properties remain consistent.

Replacement Therapy

The number of human-identical or human-analogue proteins available for replacement therapy is increasing (▶ Fig. 2.3**B**). These include native or genetically modified human insulin (see p. 256) and *erythropoietin (epoetin),* which is used to treat severe anemia (see p. 154). When these proteins are injected, they readily reach their receptors in the cell membrane. Introduction of *polyethylene glycol* (PEG) chains to certain proteins can delay their elimination from the circulation, thereby prolonging their duration of action. Metabolic diseases resulting from a lysosomal enzyme deficiency require intracellular protein delivery. Genetically engineered enzymes with a *mannose-6-phosphate residue* are suitable. This acts as the "key" for getting into the cell by receptor-mediated endocytosis and then into the interior of the lysosomes.

▶ **Protein constructs to interrupt signaling pathways (▶ Fig. 2.3C).** This is possible on both the messenger compound (C1–C3) and on the receptor side (C4–C6). The inhibitors can be classified as different "types." The expression system is given in brackets.

▶ **C1–C3.** Vascular endothelial growth factor, VEGF (see p. 377) acts through its receptors to promote the proliferation of blood vessels in the wet form of macular degeneration (the macula is the part of the retina where visual acuity is maximal → risk of blindness).

VEGF can be inactivated by:

- bevacizumab, a complete artificial antibody (see p. 376); mab: monoclonal antibody (unlicensed indication)
- the Fab antibody fragment ranibizumab
- the fusion protein aflibercept, consisting of the binding area of the VEGF receptor and an antibody Fc segment.

▶ **C4–C6.** C4–C6 show ways of interrupting the signaling pathway by receptor blockade:

- complete antibody, e.g., basiliximab (see p. 304), which counteracts interleukin 2-mediated rejection of an organ transplant
- Fab antibody fragment, e.g., abciximab, which inhibits fibrinogen-mediated platelet aggregation (see p. 166)
- Genetically engineered replication of an endogenous inactivator, e.g., interleukin1 receptor antagonist, IL-1RA, in rheumatoid arthritis (see p. 360).

▶ **Analogue products.** Imitators of the "biologics" are also keen to share in the commercial success of a product. Unlike small organic drugs, however, an exact copy of the original substance is often not possible on account of the complexity of the genetically engineered production process (cell line, nutrient medium, temperature, pressure, etc.). A structurally similar imitation is called a "biosimilar." Its benefit and risk profile must be confirmed by separate clinical trials.

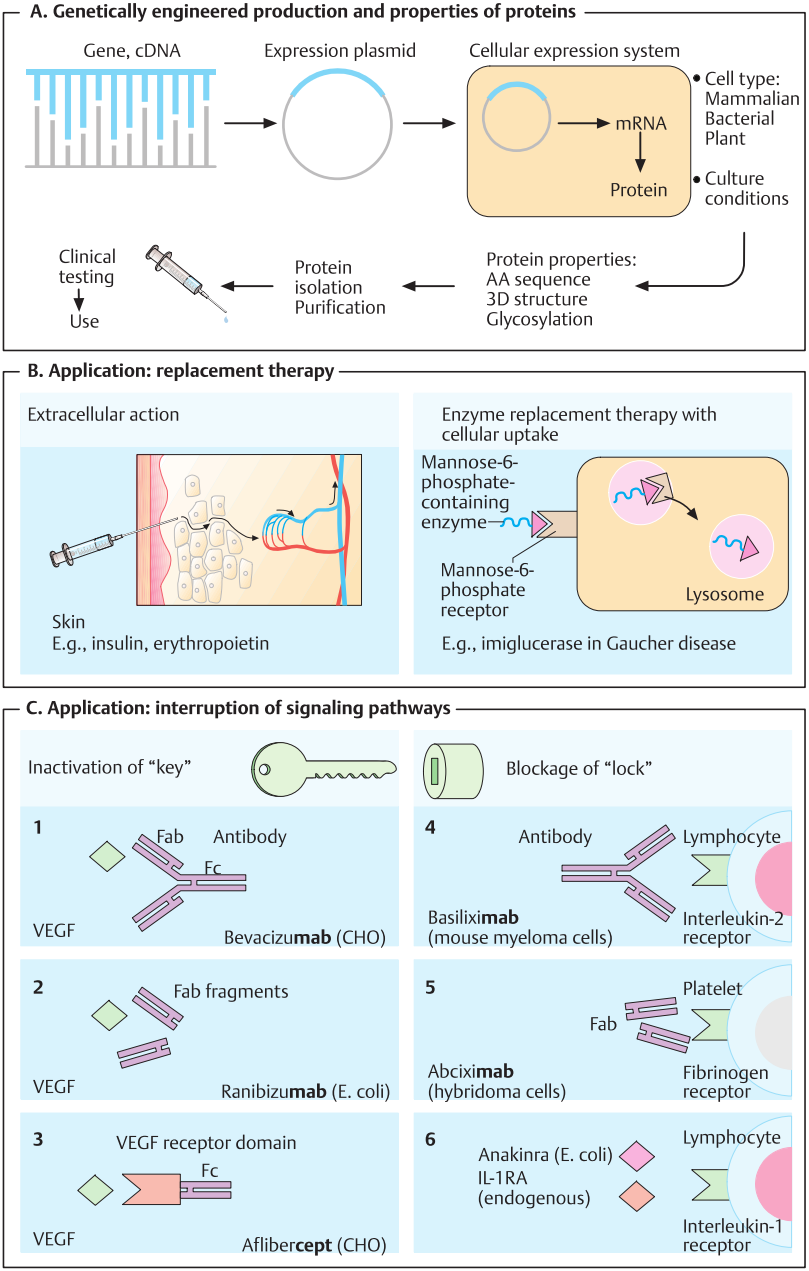

A. Genetically engineered production and properties of proteins
Gene, cDNA
Expression plasmid
Cellular expression system
mRNA
Protein
Cell type: Mammalian Bacterial Plant
Culture conditions
Protein properties: AA sequence 3D structure Glycosylation
Protein isolation Purification
Clinical testing
Use
B. Application: replacement therapy
Extracellular action
Skin
E.g., insulin, erythropoietin
Enzyme replacement therapy with cellular uptake
Mannose-6-phosphate-containing enzyme
Mannose-6-phosphate receptor
Lysosome
E.g., imiglucerase in Gaucher disease
C. Application: interruption of signaling pathways
Inactivation of "key"
Blockage of "lock"
1
Fab
Antibody
Fc
VEGF
Bevacizumab (CHO)
2
Fab fragments
VEGF
Ranibizumab (E. coli)
3
VEGF receptor domain
Fc
VEGF
Aflibercept (CHO)
4
Antibody
Lymphocyte
Basiliximab (mouse myeloma cells)
Interleukin-2 receptor
5
Platelet
Fab
Abciximab (hybridoma cells)
Fibrinogen receptor
6
Anakinra (E. coli)
IL-1RA (endogenous)
Lymphocyte
Interleukin-1 receptor

Fig. 2.3

Drug Development

The drug development process starts with the **synthesis** of novel chemical compounds. Substances with complex structures may be obtained from various sources, e.g., plants (cardiac glycosides), animal tissues (heparin), microbial cultures (penicillin G) or cultures of human cells (urokinase), or by means of gene technology (human insulin). As more insight is gained into structure–activity relationships, the search for new agents becomes more clearly focused.

Preclinical testing yields information on the biological effects of new substances. Initial screening may employ *biochemical–pharmacological investigations* (e.g., ▶ Fig. 8.3) or experiments on cell cultures, isolated cells, and isolated organs. Since these models invariably fall short of replicating complex biological processes in the intact organism, any potential drug must be tested in the whole animal. Only animal experiments can reveal whether the desired effects will actually occur at dosages that produce little or no toxicity. *Toxicological investigations* serve to evaluate the potential for: (1) toxicity associated with acute or chronic administration; (2) genetic damage (genotoxicity, mutagenicity); (3) production of tumors (oncogenicity or carcinogenicity); and (4) causation of birth defects (teratogenicity). In animals, compounds under investigation also have to be studied with respect to their absorption, distribution, metabolism, and elimination *(pharmacokinetics)*. Even at the level of preclinical testing, only a very small fraction of new compounds will prove potentially suitable for use in humans.

Pharmaceutical technology provides the methods for drug formulation.

Clinical testing starts with **Phase I** studies on healthy subjects to determine whether effects observed in animals also occur in humans. Dose–response relationships are determined. In **Phase II**, potential drugs are first tested on selected patients for therapeutic efficacy in the illness for which they are intended. If a beneficial action is evident, and the incidence of adverse effects is acceptably small, **Phase III** is entered, involving a larger group of patients in whom the new drug is compared with conventional treatments in terms of therapeutic outcome. As a form of human experimentation, these clinical trials are subject to review and approval by institutional ethics committees according to international codes of conduct (Declarations of Helsinki, Tokyo, and Venice). During clinical testing, many drugs are revealed to be unusable. Ultimately, only one new drug typically remains from some 10000 newly synthesized substances.

The decision to **approve a new drug** is made by a national regulatory body (Food and Drug Administration in the United States; the Health Protection Branch Drugs Directorate in Canada; the EU Commission in conjunction with the European Medicines Agency [EMA], London, United Kingdom) to which manufacturers are required to submit their applications. Applicants must document by means of appropriate test data (from preclinical and clinical trials) that the criteria of efficacy and safety have been met and that product forms (tablet, capsule, etc.) satisfy general standards of quality control.

Following approval, the new drug (p. 26) may be marketed under a trade name (p. 380) and so be available for prescription by physicians and dispensing by pharmacists. At this time regulatory surveillance continues in the form of postlicensing studies (**Phase IV** of clinical trials). **Pharmacovigilance** is the name given to activities intended to identify and guard against drug risks during clinical trials and subsequent marketing. This includes reporting of suspected cases of adverse drug effects (ADEs) to the national regulatory authorities. Only on the basis of long-term experience will the risk–benefit ratio be properly assessed and, thus, the therapeutic value of the new drug be determined. If the new drug offers hardly any advantage over existing ones, the cost–benefit relationship needs to be kept in mind.

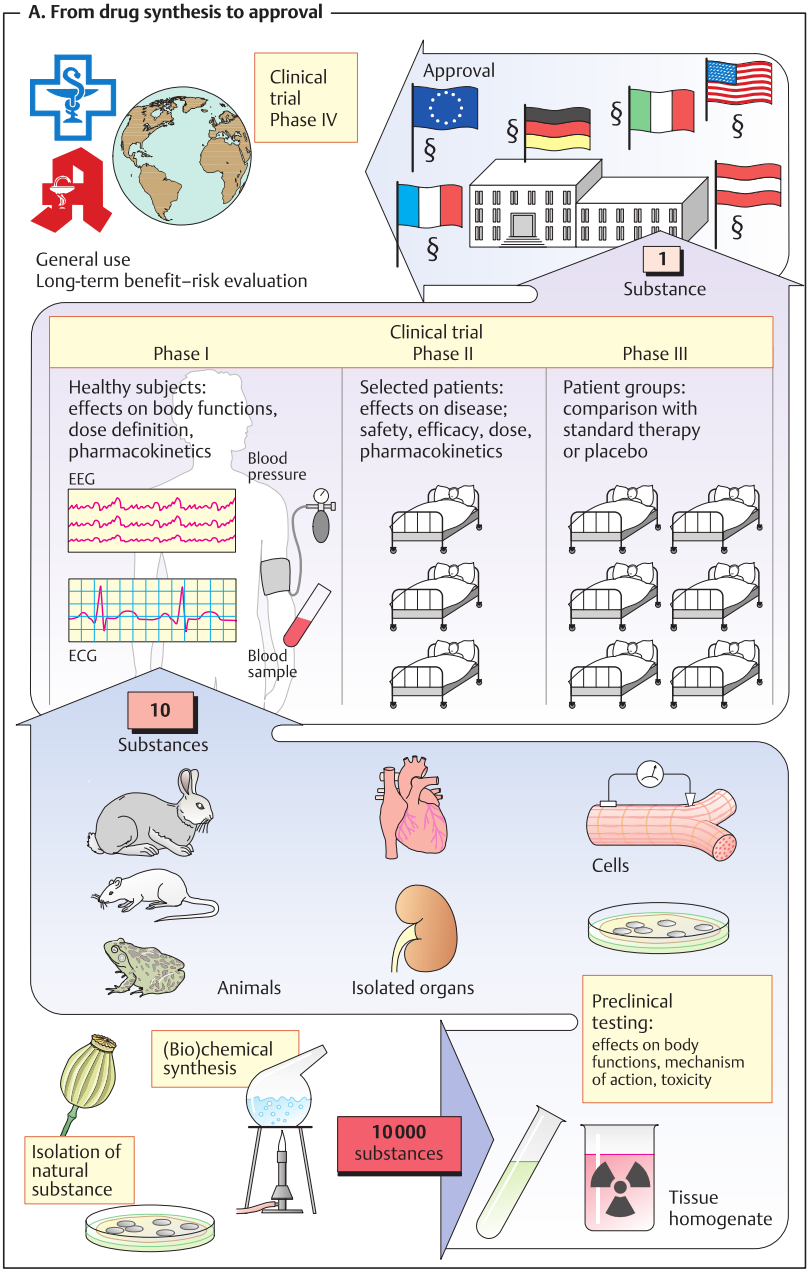

A. From drug synthesis to approval
Clinical trial Phase IV
General use
Long-term benefit–risk evaluation
Approval
1
Substance
Clinical trial
Phase I
Phase II
Phase III
Healthy subjects: effects on body functions, dose definition, pharmacokinetics
EEG
ECG
Blood pressure
Blood sample
Selected patients: effects on disease; safety, efficacy, dose, pharmacokinetics
Patient groups: comparison with standard therapy or placebo
10
Substances
Animals
Isolated organs
Cells
Preclinical testing:
effects on body functions, mechanism of action, toxicity
(Bio)chemical synthesis
Isolation of natural substance
10000 substances
Tissue homogenate

Fig. 2.4

Drug Benefit Assessment

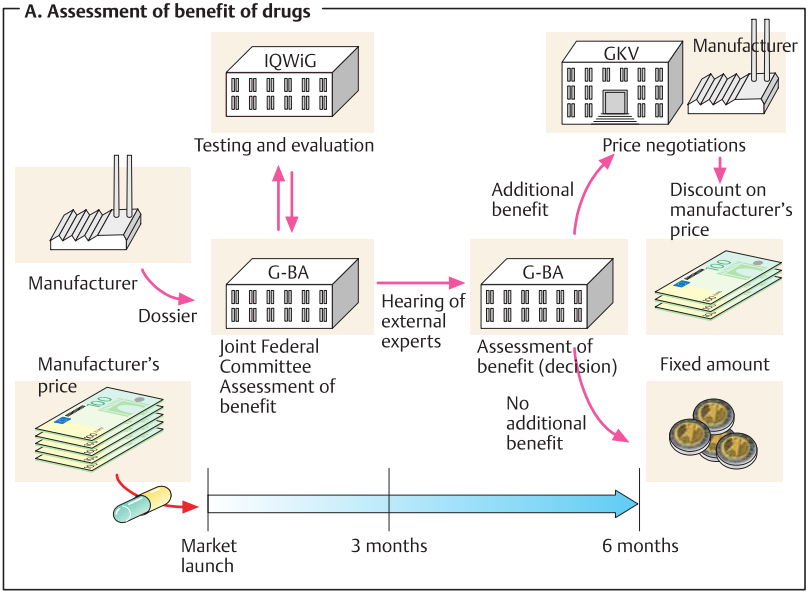
Legal Assessment of the Benefit of New Drugs

After marketing authorization for a new drug, countries have different procedures to assess the therapeutic benefit of the new compound and to adjust the drug prices accordingly. Unlike the (partially) harmonized procedures for drug approval in the US and in Europe (p. 22), the benefit assessment and price regulations differ from country to country. Due to the limited space here, we briefly illustrate the current regulations in Germany. A statutory procedure for assessing the benefit of new drugs was introduced in Germany in 2011 with a view to containing rising healthcare costs (▶ Fig. 2.5**A**). This procedure is specified in the Act for Restructuring the Pharmaceutical Market (German AMNOG). Immediately after the market launch of a new drug, the manufacturer must submit to the Joint Federal Committee (G-BA) documentation (the "dossier") showing the potential additional benefit compared with previous standard therapy. The Federal Committee receives expert advice from the Institute for Quality and Economy in Healthcare (IQWIG). Other organizations (e.g., the Medicines Committee of the German Medical Council) can comment on the submitted dossier. After three months, the G-BA decides whether the new medicine has any additional benefit and what this comprises. If there is an additional benefit compared with the previous comparative therapy, the manufacturer and National Association of Statutory Health Insurance Funds negotiate the price for the new medicine. A fixed price is specified for medicines without additional benefit.

Until December 2015, this assessment of benefit had been initiated or completed for 262 new drugs or drug combinations. No additional benefit was found in approximately 50% of the new medicines. A substantial additional benefit was confirmed for 10% and a small additional benefit for 22%. The latest information about the procedure and assessment results can be obtained on the internet on the website of the Joint Federal Committee: www.g-ba.de.

Assessment of Benefit—Number Needed to Treat

Many medicines are given to prevent later disease. Treatment of high blood pressure is an example: in itself, high blood pressure usually does not cause any symptoms, but it increases the risk for serious conditions such as myocardial infarction and stroke. Preventive drug treatment in turn is associated with a risk of adverse drug effects. The "number needed to treat" is used to quantify the expected level of benefit of a preventive measure. This states the number of persons that must be treated prophylactically for one person to derive benefit. The calculation is based on the results of clinical studies. This parameter must be strictly distinguished from the percentage risk reduction. ▶ Fig. 2.5**B** illustrates the results of a study of vertebral fracture prevention. Treatment over a number of years reduced the relative fracture risk by about 70% relative to the fracture risk in the placebo-treated control group. This ratio, however, does not identify the benefit that an individual patient can expect in statistical terms. Since the fracture event itself is relatively rare (only about one person in ten is affected in the observation period), the NNT result is 13. The remaining 12 treated persons would derive no benefit statistically—either because they would not have suffered a vertebral fracture anyway or because the medicine would not have been beneficial in the individual case. The pharmaco-economist can now calculate how much one prevented event (a fracture in this case) would cost the community of insured persons.


A. Assessment of benefit of drugs
IQWiG
Testing and evaluation
GKV
Manufacturer
Price negotiations
Additional benefit
Discount on manufacturer's price
Manufacturer
Dossier
G-BA
Joint Federal Committee Assessment of benefit
Hearing of external experts
G-BA
Assessment of benefit (decision)
Manufacturer's price
Fixed amount
No additional benefit
Market launch
3 months
6 months

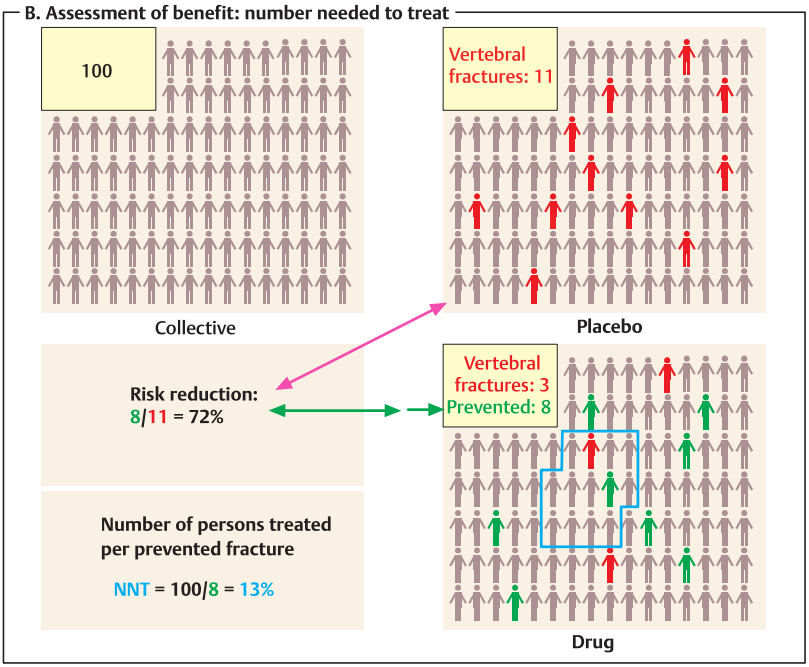

B. Assessment of benefit: number needed to treat
100
Collective
Vertebral fractures: 11
Placebo
Risk reduction:
8/11 = 72%
Vertebral fractures: 3
Prevented: 8
Number of persons treated per prevented fracture
NNT = 100/8 = 13%
Drug

Fig. 2.5

Congeneric Drugs and Name Diversity

The preceding pages outline the route leading to approval of a new drug. The pharmaceutical receives an **International Nonproprietary Name** (INN) and a brand or trade name chosen by the pharmaceutical company. Patent protection enables the patent holder to market the new substance for a specified period of time. As soon as the patent protection expires, the drug concerned can be put on the market as a generic under a nonproprietary name or as a successor preparation under other brand names. When successor preparations of biopharmaceuticals (such as epoetin or somatotropin) are put on the market, they are called **biosimilars**. These products must meet particularly high requirements with regard to bioequivalence and side effects. Since patent protection is generally already sought during the development phase, sale of the drug may be protected only for a few years.

The value of a **new drug** depends on whether it involves a novel active principle or merely an analogue (or congeneric) preparation with a slightly changed chemical structure. It is of course much more arduous to develop a substance that possesses a novel mechanism of action and thereby expands therapeutic possibilities. Examples of such fundamental innovations from recent years include the kinase inhibitors (e.g., imatinib, p. 300), HIV adsorption and integrase inhibitors (p. 288), and incretin mimetics (p. 262).

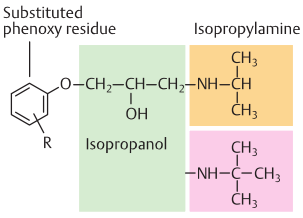
Much more frequently, "new drugs" are analogue substances that imitate the chemical structure of a successful pharmaceutical. These compounds contain the requisite features in their molecule but differ from the parent molecule by structural alterations that are biologically irrelevant. Such **analogue substances**, or "me-too" products, do not add anything new regarding the mechanism of action. The β-blockers are an example of the overabundance of analogue substances: about 20 individual substances with the same pharmacophoric groups differing only in the substituents at the phenoxy residue. This entails small differences in pharmacokinetic behavior and relative affinity for β-receptor subtypes (examples shown in **A**). A small fraction of these substances would suffice for therapeutic use. The WHO Model List of Essential Medicines names only three β-blockers (bisoprolol, propranolol, timolol) from the existing profusion (▶ Fig. 2.6**A**). The corresponding phenomenon is evident among various other drug groups (e.g., benzodiazepines, nonsteroidal anti-inflammatory agents, and cephalosporins). Most analogue substances can be neglected.

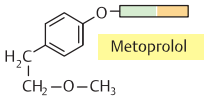
After patent protection expires, competing drug companies will at once market successful (i.e., profitable) pharmaceuticals as second-submission **successor** (or "follow-on") **preparations**. Since no research expenses are involved at this point, successor drugs can be offered at a cheaper price, either as **generics** (INN + pharmaceutical company name) or under new fancy names. Thus some common drugs circulate under many different trade names. An extreme example is presented in **B** for the analgesic ibuprofen.

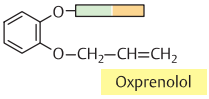
The excess of analogue preparations and the unnecessary diversity of trade names for one and the same drug make the pharmaceutical markets of some countries (e.g., Germany) rather perplexing. A critical listing of **essential drugs** is a prerequisite for optimal pharmacotherapy and would be of great value for medical practice.

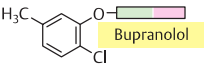
Another sales strategy of the pharmaceutical industry can complicate matters for the prescribing physician, by combining a necessary drug with an indifferent or low-dose second substance. For instance, analgesics are combined with a little caffeine (about as much as in a cup of coffee) or vitamin C (as much as in one tomato), a new trade name is invented, and the price is raised.

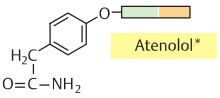
A. β-Blockers of similar basic structure

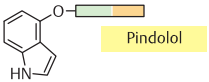


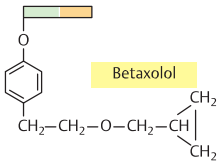


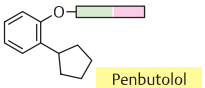


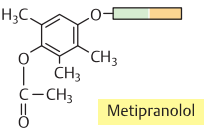


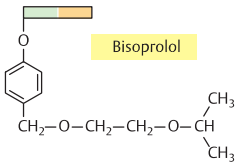


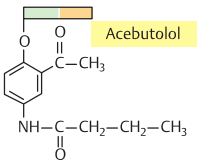


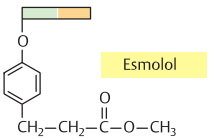


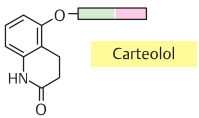


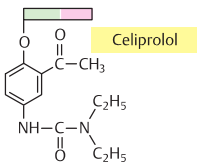


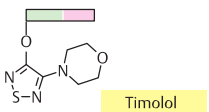


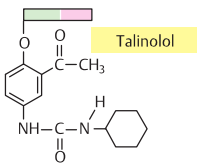


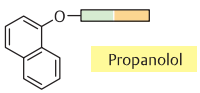


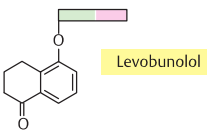












The nebivolol and carvedilol molecules are more complicated.

B. Successor preparations for a pharmaceutical (2014)

Ibuprofen under different trade names, introduced as Brufen® (no longer available in some countries): 259 products from 36 companies (in Germany)

Fig. 2.6

Oral Dosage Forms

The **coated tablet** contains a drug within a core that is covered by a shell, e.g., wax coating, that serves (1) to protect perishable drugs from decomposing, (2) to mask a disagreeable taste or odor, (3) to facilitate passage on swallowing, or (4) to permit color coding.

Capsules usually consist of an oblong casing —generally made of gelatin—that contains the drug in powder or granulated form.

In the **matrix-type tablet**, the drug is embedded in an inert meshwork, from which it is released by diffusion upon being moistened. In contrast to *solutions*, which permit direct absorption of drug (▶ Fig. 3.1**A**, track 3), the use of solid dosage forms initially requires *tablets* to break up and *capsules* to open (**disintegration**), before the drug can be dissolved (**dissolution**) and pass through the gastrointestinal mucosal lining (**absorption**). Because disintegration of the tablet and dissolution of the drug take time, absorption will occur mainly in the intestine (▶ Fig. 3.1**A**, track 2). In the case of a solution, absorption already starts in the stomach (▶ Fig. 3.1**A**, track 3).

For acid-labile drugs, a coating of wax or of a cellulose acetate polymer is used to prevent disintegration of solid dosage forms in the stomach. Accordingly, disintegration and dissolution will take place in the duodenum at normal rate (▶ Fig. 3.1**A**, track 1) and drug liberation per se is not retarded.

The **liberation** of drug, and hence the site and time-course of absorption, are subject to modification by appropriate production methods for matrix-type tablets, coated tablets, and capsules. In the case of the matrix tablet, this is done by incorporating the drug into a lattice from which it can be slowly leached out by gastrointestinal fluids. As the matrix tablet undergoes enteral transit, drug liberation and absorption proceed en route (▶ Fig. 3.1**A**, track 4). In the case of coated tablets, coat thickness can be designed such that release and absorption of drug occur either in the proximal (▶ Fig. 3.1**A**, track 1) or distal (▶ Fig. 3.1**A**, track 5) bowel. Thus, by matching dissolution time with small-bowel transit time, drug release can be timed to occur in the colon.

Drug liberation and, hence, absorption can also be spread out when the drug is presented in the form of granules consisting of pellets coated with a waxy film of graded thickness. Depending on film thickness, gradual dissolution occurs during enteral transit, releasing drug at variable rates for absorption. The principle illustrated for a *capsule* can also be applied to tablets. In this case, either drug pellets coated with films of various thicknesses are compressed into a tablet or the drug is incorporated into a *matrix-type* tablet. In contrast to timed-release capsules *slow-release tablets* have the advantage of being divisible ad libitum; thus fractions of the dose contained within the entire tablet may be administered.

This kind of **retarded drug release** is employed when a rapid rise in blood levels of drug is undesirable, or when absorption is being slowed in order to prolong the action of drugs that have a short sojourn in the body.

A. Oral administration: drug release and absorption

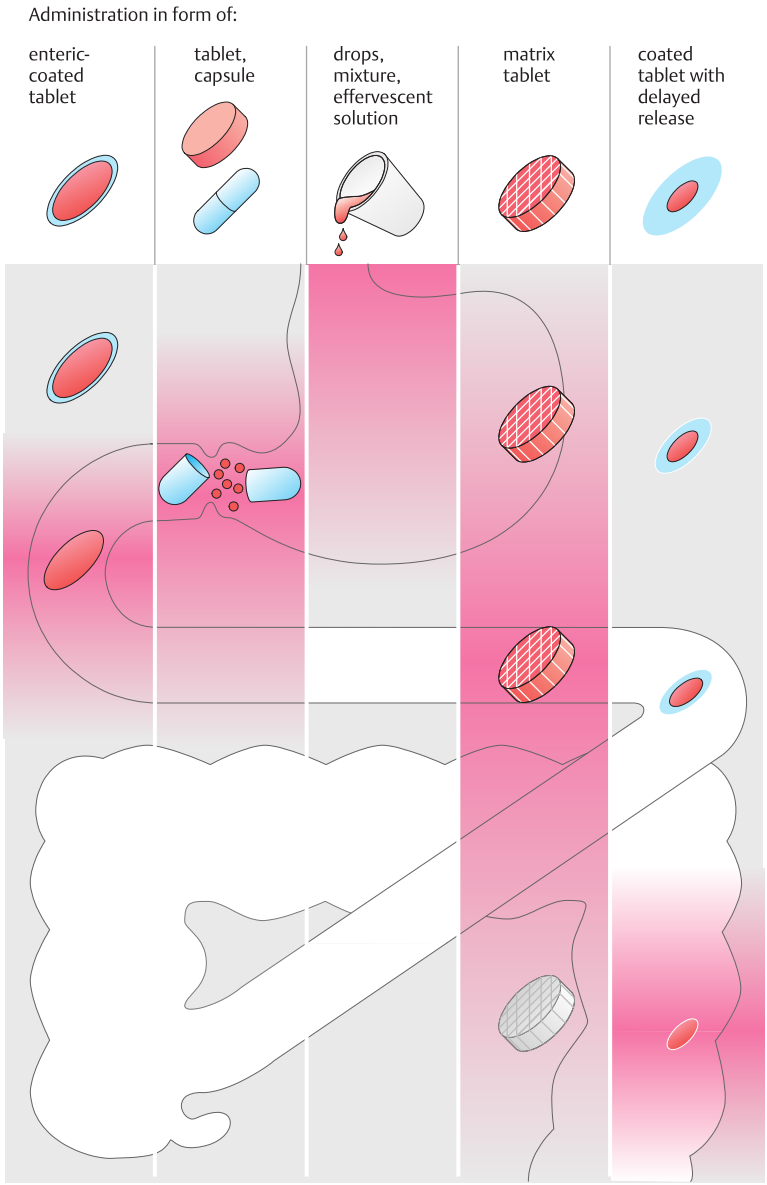


Fig. 3.1

Drug Administration by Inhalation

Inhalation in the form of an aerosol, a gas, or a mist permits drugs to be delivered to the bronchial mucosa and, to a lesser extent, to the alveolar membranes. This route is chosen for drugs intended to affect bronchial smooth muscle or the consistency of bronchial mucus. Furthermore, gaseous or volatile agents can be administered by inhalation with the goal of alveolar absorption and systemic effects (e.g., inhalational anesthetics, p. 218). **Aerosols** are formed when a drug solution or micronized powder is converted into a mist or dust, respectively.

In conventional sprays (e.g., nebulizer), the air jet required for the aerosol formation is generated by the stroke of a pump. Alternatively, the drug is delivered from a solution or powder packaged in a pressurized canister equipped with a valve through which a metered dose is discharged. During use, the inhaler (spray dispenser) is held directly in front of the mouth and actuated at the start of inspiration. The effectiveness of delivery depends on the position of the device in front of the mouth, the size of the aerosol particles, and the coordination between opening the spray valve and inspiration. The size of the aerosol particles determines the speed at which they are swept along by inhaled air, and hence the **depth of penetration into the respiratory tract**. Particles >100 µm in diameter are trapped in the oropharyngeal cavity; those having diameters between 10 and 60 µm will be deposited on the epithelium of the bronchial tract. Particles <2 µm in diameter can reach the alveoli, but they will be exhaled again unless they settle out.

Drug deposited on the mucous lining of the bronchial epithelium is partly absorbed and partly transported with bronchial mucus toward the larynx. Bronchial mucus travels upward owing to the orally directed undulatory beat of the epithelial cilia. Physiologically, this mucociliary transport functions to remove inspired dust particles.

Thus, only a portion of the drug aerosol (~10%) gains access to the respiratory tract and just a fraction of this amount penetrates the mucosa, whereas the remainder of the aerosol undergoes mucociliary transport to the laryngopharynx and is swallowed. The advantage of inhalation (i.e., localized administration without systemic load) is fully exploited by using drugs that are poorly absorbed from the intestine (tiotropium, cromolyn) or are subject to first-pass elimination (p. 60); for example, glucocorticoids such as beclomethasone dipropionate, budesonide, flunisolide, and fluticasone dipropionate or β-agonists such as salbutamol and fenoterol.

Even when the swallowed portion of an inhaled drug is absorbed in unchanged form, administration by this route has the advantage that drug concentrations at the bronchi will be higher than in other organs.

The efficiency of mucociliary transport depends on the force of kinociliary motion and the viscosity of bronchial mucus. Both factors can be altered pathologically (e.g., by smoker's cough or chronic bronchitis).

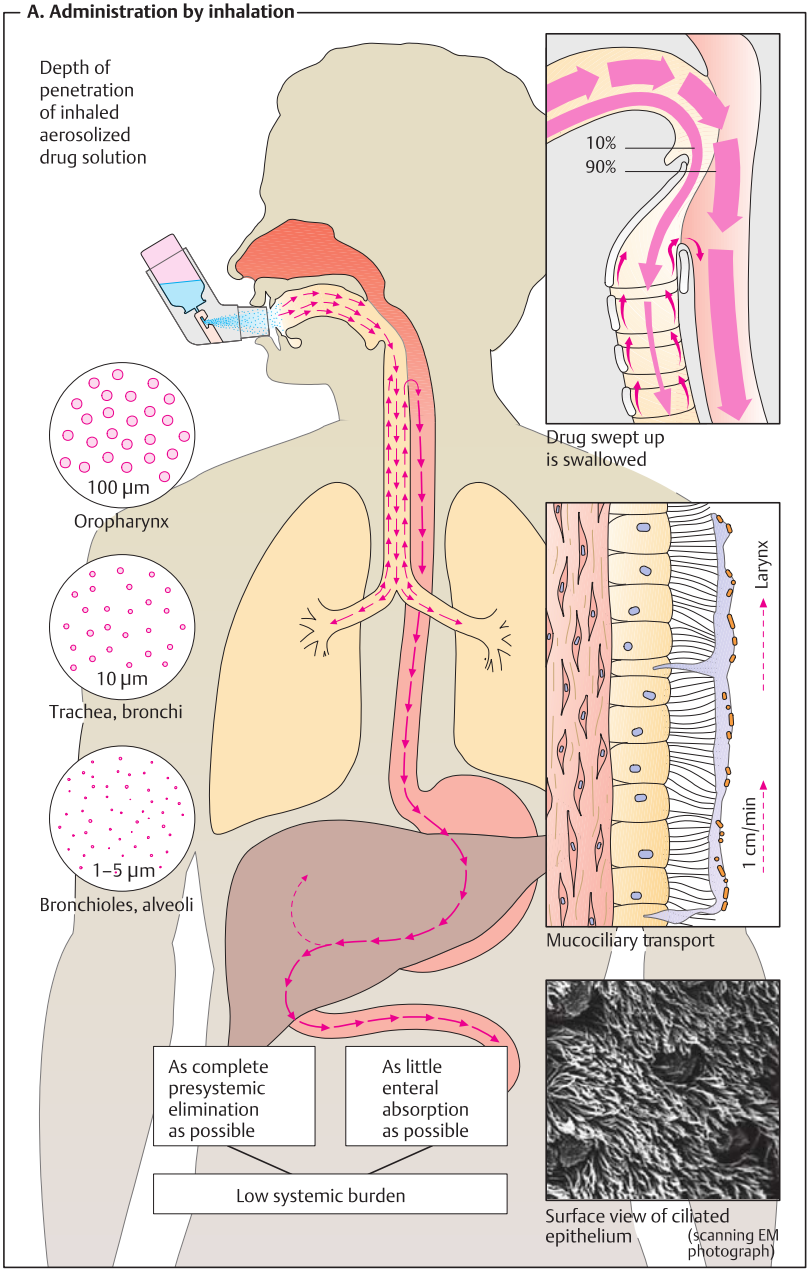

A. Administration by inhalation
Depth of penetration of inhaled aerosolized drug solution
100 µm
Oropharynx
10 µm
Trachea, bronchi
1–5 µm
Bronchioles, alveoli
10%
90%
Drug swept up is swallowed
Larynx
1 cm/min
Mucociliary transport
Surface view of ciliated epithelium
(scanning EM photograph)
As complete presystemic elimination as possible
As little enteral absorption as possible
Low systemic burden

Fig. 3.2

Dermatological Agents

Pharmaceutical preparations applied to the outer skin are intended either to provide skin care and protection from noxious influences (▶ Fig. 3.3**A**) or to serve as a vehicle for drugs that are to be absorbed into the skin or, if appropriate, into the general circulation (▶ Fig. 3.3**B**).

Skin Protection

Protective agents (▶ Fig. 3.3**A**) are of several kinds to meet different requirements according to skin condition (dry, low in oil, chapped vs. moist, oily, elastic), and the type of noxious stimuli (prolonged exposure to water, regular use of alcohol-containing disinfectants, intense solar irradiation). Distinctions among protective agents are based upon consistency, physicochemical properties (lipophilic, hydrophilic), and the presence of additives.

▶ **Dusting powders.** Dusting powders are sprinkled onto the intact skin and consist of talc, magnesium stearate, silicon dioxide (silica), or starch. They adhere to the skin, forming a low-friction film that attenuates mechanical irritation. Powders exert a drying (evaporative) effect.

▶ **Lipophilic ointment (oil ointment).** Lipophilic ointment consists of a lipophilic base (paraffin oil, petroleum jelly, lanolin) and may contain up to 10% powder materials, such as zinc oxide, titanium oxide, starch, or a mixture of these. Emulsifying ointments are made of paraffins and an emulsifying wax, and are miscible with water.

▶ **Paste (oil paste).** Paste is an ointment containing more than 10% pulverized constituents.

▶ **Lipophilic (oily) cream.** Lipophilic cream is an emulsion of water in oil, easier to spread than oil paste or oil ointment.

▶ **Hydrogel and water-soluble ointment.** These substances achieve their consistency by means of different gel-forming agents (gelatin, methylcellulose, polyethylene glycol). **Lotions** are aqueous suspensions of water-insoluble and solid constituents.

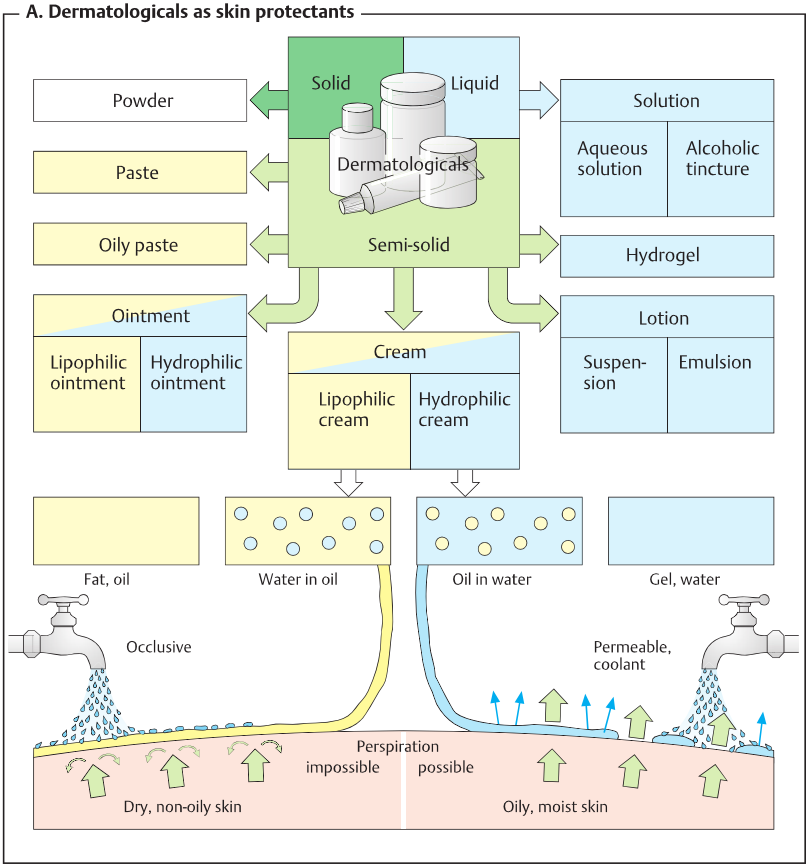
▶ **Hydrophilic (aqueous) cream.** Hydrophilic cream is an oil-in-water emulsion formed with the aid of an emulsifier; it may also be considered an oil-in-water emulsion of an emulsifying ointment.

All dermatological agents having a lipophilic base adhere to the skin as a water-repellent coating. They do not wash off and they also prevent (**occlude**) outward passage of water from the skin. The skin is protected from drying, and its hydration and elasticity increase.

Diminished evaporation of water results in warming of the occluded skin. Hydrophilic agents wash off easily and do not impede transcutaneous output of water. Evaporation of water is felt as a cooling effect.

Dermatological Agents as Vehicles

In order to reach its site of action, a drug must leave its pharmaceutical preparation (▶ Fig. 3.3**B**) and enter the skin if a local effect is desired (e.g., glucocorticoid ointment), or be able to penetrate it if a systemic action is intended (transdermal delivery system, e.g., nitroglycerin patch, p. 138). The tendency for the drug to leave the drug vehicle is higher the more the drug and vehicle differ in lipophilicity (high tendency: hydrophilic drug and lipophilic vehicle; and vice versa). Because the skin represents a closed lipophilic barrier (p. 38), only lipophilic drugs are absorbed. Hydrophilic drugs fail to penetrate the outer skin even when applied in a lipophilic vehicle. This formulation can be useful when high drug concentrations are required at the skin surface (e.g., neomycin ointment for bacterial skin infections).


A. Dermatologicals as skin protectants
Powder
Solid
Liquid
Solution
Aqueous solution
Alcoholic tincture
Paste
Dermatologicals
Oily paste
Semi-solid
Hydrogel
Ointment
Lipophilic ointment
Hydrophilic ointment
Cream
Lipophilic cream
Hydrophilic cream
Lotion
Suspen-sion
Emulsion
Fat, oil
Water in oil
Oil in water
Gel, water
Occlusive
Permeable, coolant
Perspiration
impossible
possible
Dry, non-oily skin
Oily, moist skin

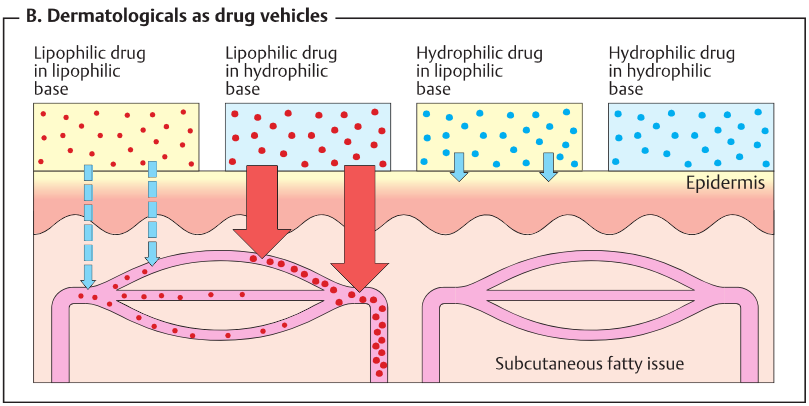

B. Dermatologicals as drug vehicles
Lipophilic drug in lipophilic base
Lipophilic drug in hydrophilic base
Hydrophilic drug in lipophilic base
Hydrophilic drug in hydrophilic base
Epidermis
Subcutaneous fatty issue

Fig. 3.3

From Administration to Distribution in the Body

As a rule, drugs reach their target organs via the blood. Therefore, they must first enter the blood, usually in the venous limb of the circulation. There are several possible sites of entry.

The drug may be injected or infused **intravenously**, in which case it is introduced directly into the bloodstream. In **subcutaneous** or **intramuscular** injection, the drug has to diffuse from its site of administration into the blood. Because these procedures entail injury to the outer skin, strict requirements must be met concerning technique. For this reason, the **oral** route (i.e., simple administration by mouth) involving subsequent uptake of drug across the gastrointestinal mucosa into the blood is chosen much more frequently. The disadvantage of this route is that the drug must pass through the liver on its way into the general circulation. In all of the above modes of administration, this fact assumes practical significance for any drug that may be rapidly transformed or possibly inactivated in the liver (first-pass effect, presystemic elimination, p. 60; bioavailability). Furthermore, a drug has to traverse the lungs before entering the general circulation. Pulmonary tissues may trap hydrophobic substances. The lungs may then act as a buffer and thus prevent a rapid rise in drug levels in peripheral blood after i.v. injection (important, for example, with i.v. anesthetics). Even with rectal administration, at least a fraction of the drug enters the general circulation via the portal vein, because only blood from the short terminal segment of the rectum drains directly into the inferior vena cava. Hepatic passage is circumvented when absorption occurs buccally or sublingually, because venous blood from the oral cavity drains into the superior vena cava. The same would apply to administration by **inhalation** (p. 30). However, with this route, a local effect is usually intended, and a systemic action is intended only in exceptional cases. Under certain conditions, drug can also be applied percutaneously in the form of a **transdermal** delivery system. In this case, drug is released from the reservoir at constant rate over many hours, and then penetrates the epidermis and subepidermal connective tissue where it enters blood capillaries. Only a very few drugs can be applied transdermally. The feasibility of this route is determined by both the physicochemical properties of the drug and the therapeutic requirements (acute vs. long-term effect).

Speed of absorption is determined by the route and method of administration. It is *fastest* with *intravenous injection, less fast* with *intramuscular injection,* and *slowest* with *subcutaneous injection.* When the drug is applied to the oral mucosa (**buccal**, **sublingual** routes), plasma levels rise faster than with conventional oral administration because the drug preparation is deposited at its actual site of absorption and very high concentrations in saliva occur upon the dissolution of a single dose. Thus, uptake across the oral epithelium is accelerated. Furthermore, drug absorption from the oral mucosa avoids passage through the liver and, hence, presystemic elimination. The buccal or sublingual route is not suitable for poorly water-soluble or poorly absorbable drugs. Such agents should be given orally because both the volume of fluid for dissolution and the absorbing surface are much larger in the small intestine than in the oral cavity.

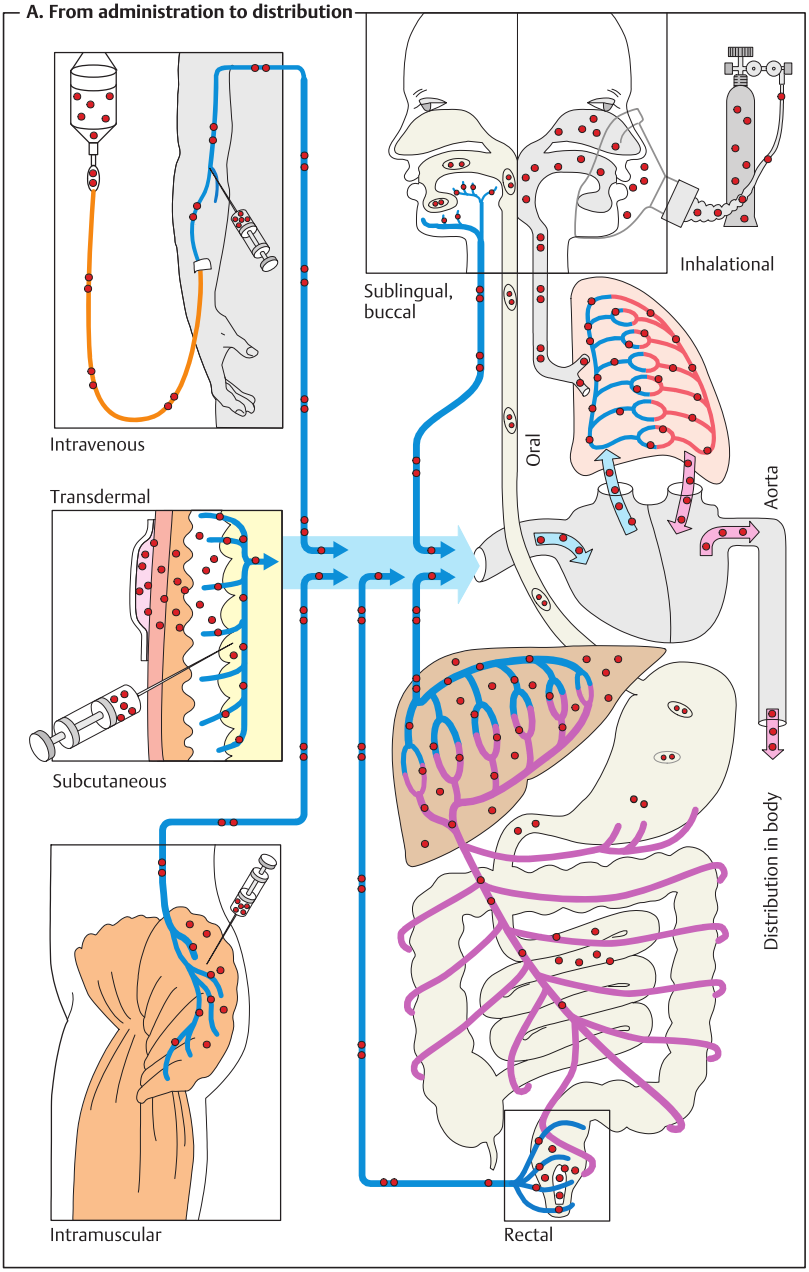

A. From administration to distribution
Intravenous
Transdermal
Subcutaneous
Intramuscular
Sublingual, buccal
Inhalational
Oral
Aorta
Distribution in body
Rectal

Fig. 3.4

Potential Targets of Drug Action

Drugs are designed to exert a selective influence on vital processes in order to alleviate or eliminate symptoms of disease. The smallest basic unit of an organism is the **cell**. The outer cell membrane, or plasmalemma, effectively demarcates the cell from its surroundings, thus permitting a large degree of internal autonomy. Embedded in the plasmalemma are **transport proteins** that serve to mediate *controlled metabolic exchange with the cellular environment*. These include energy-consuming pumps (e.g., Na^+/K^+-ATPase, p. 148), carriers (e.g., for Na^+/glucose cotransport), and ion channels (e.g., for sodium [p. 150] or calcium [p. 140]) (▶ Fig. 4.1**A** 1).

Functional coordination between single cells is a prerequisite for the viability of the organism, hence also the survival of individual cells. Cell functions are coordinated by means of cytosolic contacts between neighboring cells (gap junctions, e.g., in the myocardium) and messenger substances for the transfer of information. Included among these are transmitters released from nerves, which the cell is able to recognize with the help of specialized membrane binding sites or **receptors**. Hormones secreted by endocrine glands into the blood, then into the extracellular fluid, represent another class of chemical signals. Finally, signaling substances can originate from neighboring cells: paracrine regulation, for instance by the prostaglandins (p. 198) and cytokines.

The **effect of a drug** frequently results from interference with cellular function. Receptors for the recognition of endogenous transmitters are obvious sites of drug action (receptor agonists and antagonists, p. 78). Altered activity of membrane transport systems affects cell function (e.g., cardiac glycosides, p. 148; loop diuretics, p. 178; calcium antagonists, p. 140). Drugs may also directly interfere with intracellular metabolic processes, for instance by inhibiting (phosphodiesterase inhibitors, p. 136) or activating (organic nitrates, p. 138) an enzyme (▶ Fig. 4.1**A** 2); even processes in the cell nucleus can be affected (e.g., DNA damage by certain cytostatics).

In contrast to drugs acting from the outside on cell membrane constituents, agents acting in the cell's interior need to penetrate the cell membrane.

The **cell membrane** basically consists of a **phospholipid bilayer** (50 Å = 5 nm in thickness), embedded in which are proteins (integral membrane proteins, such as receptors and transport molecules). Phospholipid molecules contain two long-chain *fatty acids* in ester linkage with two of the three hydroxyl groups of *glycerol.* Bound to the third hydroxyl group is *phosphoric acid,* which, in turn, carries a further *residue,* e.g., choline (phosphatidylcholine = lecithin), the amino acid serine (phosphatidylserine), or the cyclic polyhydric alcohol inositol (phosphatidylinositol). In terms of solubility, phospholipids are amphiphilic: the tail region containing the apolar fatty acid chains is lipophilic; the remainder—the polar head—is hydrophilic. By virtue of these properties, phospholipids aggregate spontaneously into a bilayer in an aqueous medium, their polar heads being directed outward into the aqueous medium, the fatty acid chains facing each other and projecting into the inside of the membrane (▶ Fig. 4.1**A** 3).

The **hydrophobic interior** of the phospholipid membrane constitutes a diffusion barrier virtually impermeable to charged particles. Apolar particles, however, are better able to penetrate the membrane. This is of major importance with respect to the absorption, distribution, and elimination of drugs.

A. Site at which drugs act to modify cell function

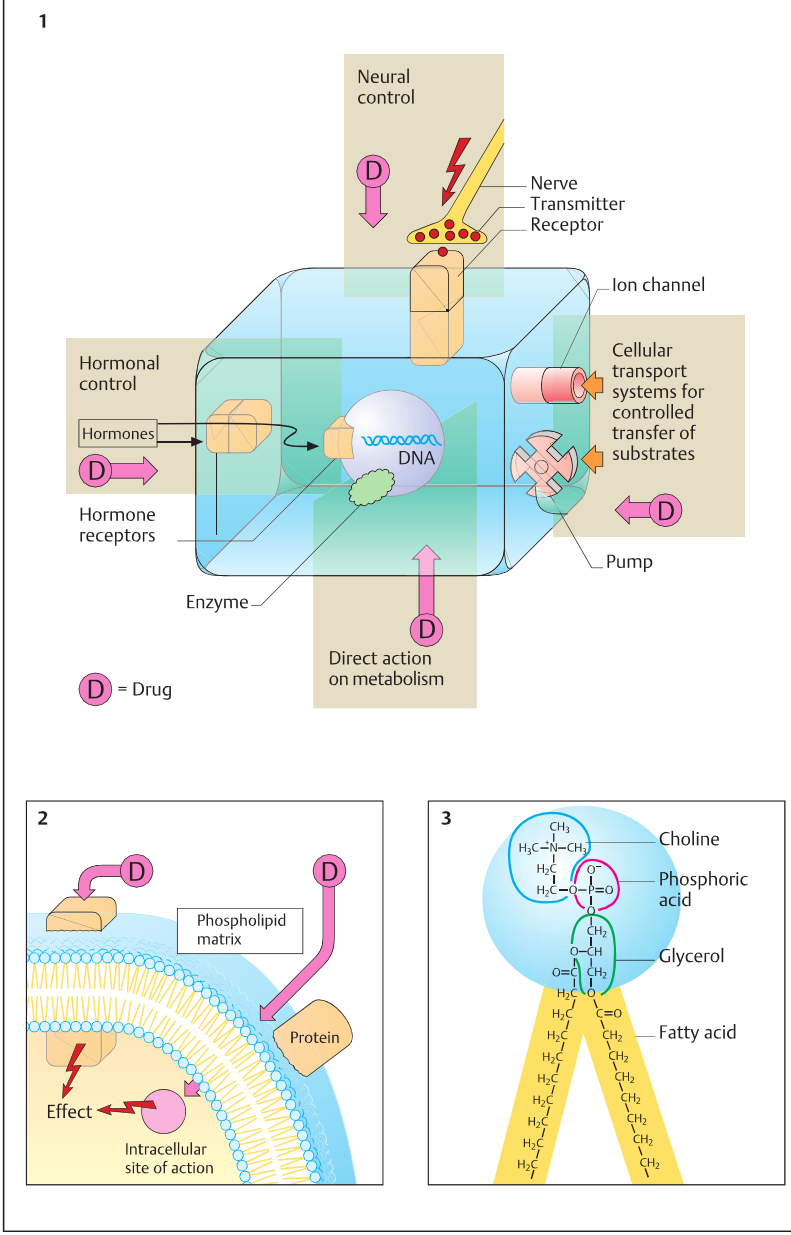


Fig. 4.1

External Barriers of the Body

Prior to its uptake into the blood (i.e., during absorption), the drug has to overcome barriers that demarcate the body from its surroundings, that is, that separate the internal from the external milieu. These boundaries are formed by the skin and mucous membranes.

When absorption takes place in the **gut** (enteral absorption), the intestinal epithelium is the barrier. This single-layered epithelium is made up of enterocytes, with a brush border (microvilli) to increase surface area, and mucus-producing goblet cells. On their luminal side, these cells are joined together by *zonulae occludentes* (indicated by black dots in the inset, bottom left). A *zonula occludens*, or tight junction, is a region in which the phospholipid membranes of two cells establish close contact and become joined via integral membrane proteins (semicircular inset, left center). The region of fusion surrounds each cell like a ring such that neighboring cells are welded together in a continuous belt. In this manner, an unbroken phospholipid layer is formed (yellow area in the schematic drawing, bottom left) and acts as a continuous barrier between the two spaces separated by the cell layer—in the case of the gut—the intestinal lumen (dark blue) and interstitial space (light blue). The efficiency with which such a barrier restricts exchange of substances can be increased by arranging these occluding junctions in multiple arrays, as for instance in the endothelium of cerebral blood vessels. The connecting proteins (connexins) furthermore serve to restrict mixing of other functional membrane proteins (carrier molecules, ion pumps, ion channels) that occupy specific apical or basolateral areas of the cell membrane.

This phospholipid bilayer represents the intestinal mucosa–blood barrier that a drug must cross during enteral absorption. Eligible drugs are those whose physicochemical properties allow permeation through the lipophilic membrane interior (yellow) or that are subject to a special inwardly directed carrier transport mechanism. Conversely, drugs can undergo backtransport into the gut by means of efflux pumps (P-glycoprotein) located in the luminal membrane of the intestinal epithelium. Absorption of such drugs proceeds rapidly because the absorbing surface is greatly enlarged owing to the formation of the epithelial brush border (submicroscopic foldings of the plasmalemma). The absorbability of a drug is characterized by the *absorption quotient*, that is, the amount absorbed divided by the amount in the gut available for absorption.

In the **respiratory tract**, cilia-bearing epithelial cells are also joined on the luminal side by zonulae occludentes, so that the bronchial space and the interstitium are separated by a continuous phospholipid barrier.

With sublingual or buccal administration, the drug encounters the nonkeratinized, multilayered squamous epithelium of the **oral mucosa**. Here, the cells establish punctate contacts with each other in the form of desmosomes (not shown); however, these do not seal the intercellular clefts. Instead, the cells have the property of sequestering polar lipids that assemble into layers within the extracellular space (semicircular inset, center right). In this manner, a continuous phospholipid barrier arises also inside squamous epithelia, although at an extracellular location, unlike that of intestinal epithelia. A similar barrier principle operates in the multilayered keratinized squamous epithelium of the **skin**.

The presence of a continuous phospholipid layer again means that only lipophilic drugs can enter the body via squamous epithelia. Epithelial thickness, which in turn depends on the depth of the stratum corneum, determines the extent and speed of absorption. Examples of drugs that can be conveyed via the skin into the blood include scopolamine (p. 126), nitroglycerin (p. 138), fentanyl (p. 214), and the gonadal hormones (p. 246). Toxic substances that are sufficiently lipophilic can also be absorbed through the skin to cause percutaneous poisoning. Examples include benzene, chlorinated dibenzodioxins, and organophosphates.

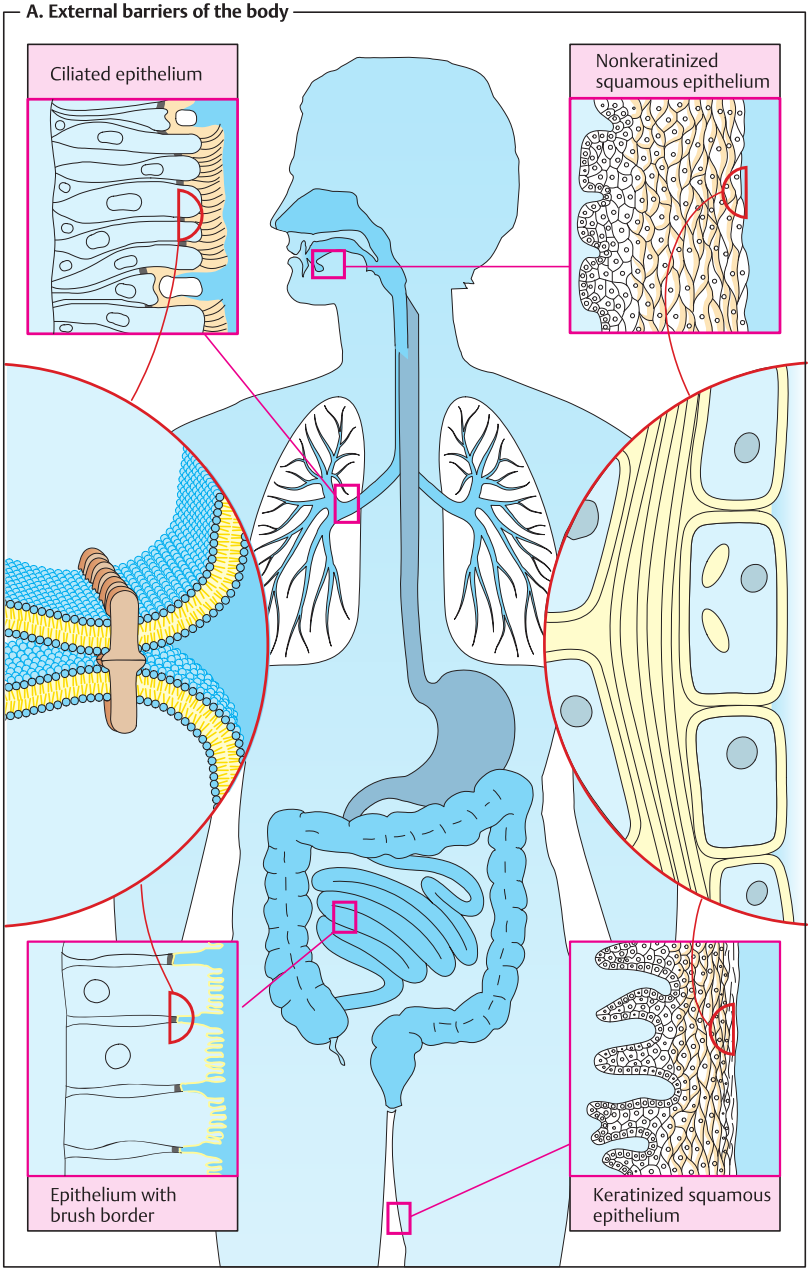

A. External barriers of the body
Ciliated epithelium
Nonkeratinized squamous epithelium
Epithelium with brush border
Keratinized squamous epithelium

Fig. 5.1

Blood–Tissue Barriers

Drugs are transported in the blood to different tissues of the body. In order to reach their sites of action, they must leave the bloodstream. Drug permeation occurs largely in the capillary bed, where both surface area and time available for exchange are maximal (extensive vascular branching, low velocity of flow). The capillary wall forms the blood–tissue barrier. Basically, this consists of an endothelial cell layer and a basement membrane enveloping the latter (solid black line in the schematic drawings). The endothelial cells are "riveted" to each other by tight junctions or occluding zonulae (labeled Z in the electron micrograph, upper left) such that no clefts, gaps, or pores remain that would permit drugs to pass unimpeded from the blood into the interstitial fluid.

The blood–tissue barrier is developed differently in the various capillary beds. Permeability of the capillary wall to drugs is determined by the structural and functional characteristics of the endothelial cells. In many capillary beds, e.g., those of **cardiac muscle**, endothelial cells are characterized by pronounced **endocytotic** and **transcytotic** activity, as evidenced by numerous invaginations and vesicles (arrows in the electron micrograph, upper right). Transcytotic activity entails transport of fluid or macromolecules from the blood into the interstitium and vice versa. Any solutes trapped in the fluid, including drugs, may traverse the blood–tissue barrier. In this form of transport, the physicochemical properties of drugs are of little importance.

In some capillary beds (e.g., in the **pancreas**), endothelial cells exhibit **fenestrations**. Although the cells are tightly connected by continuous junctions, they possess pores (arrows in electron micrograph, lower left) that are closed only by diaphragms. Both the diaphragm and basement membrane can be readily penetrated by substances of low molecular weight—the majority of drugs—but less so by macromolecules, e.g., proteins such as insulin (G: insulin storage granule). Penetrability of macromolecules is determined by molecular size and electric charge. Fenestrated endothelia are found in the capillaries of the *gut* and *endocrine glands.*

In the central nervous system (**brain** and **spinal cord**), capillary endothelia lack pores and there is little transcytotic activity. In order to cross the **blood–brain barrier**, drugs must diffuse transcellularly, i.e., penetrate the luminal and basal membrane of endothelial cells. Drug movement along this path (p. 42) requires specific physicochemical properties or the presence of a transport mechanism, e.g., L-dopa (p. 334). Thus, the blood–brain barrier is permeable only to certain types of drugs.

Drugs exchange freely between blood and interstitium in the liver, where endothelial cells exhibit large fenestrations (100 nm in diameter) facing Disse spaces (D) and where neither diaphragms nor basement membranes impede drug movement.

Diffusion barriers are also present beyond the capillary wall; e.g., *placental barrier* of fused syncytiotrophoblast cells; *blood–testicle barrier,* junctions interconnecting Sertoli cells; brain *choroid plexus–blood barrier,* occluding junctions between ependymal cells.

(Vertical bars in the electron micrographs represent 1 µm; E, cross-sectioned erythrocyte; AM, actomyosin; G, insulin-containing granules.)

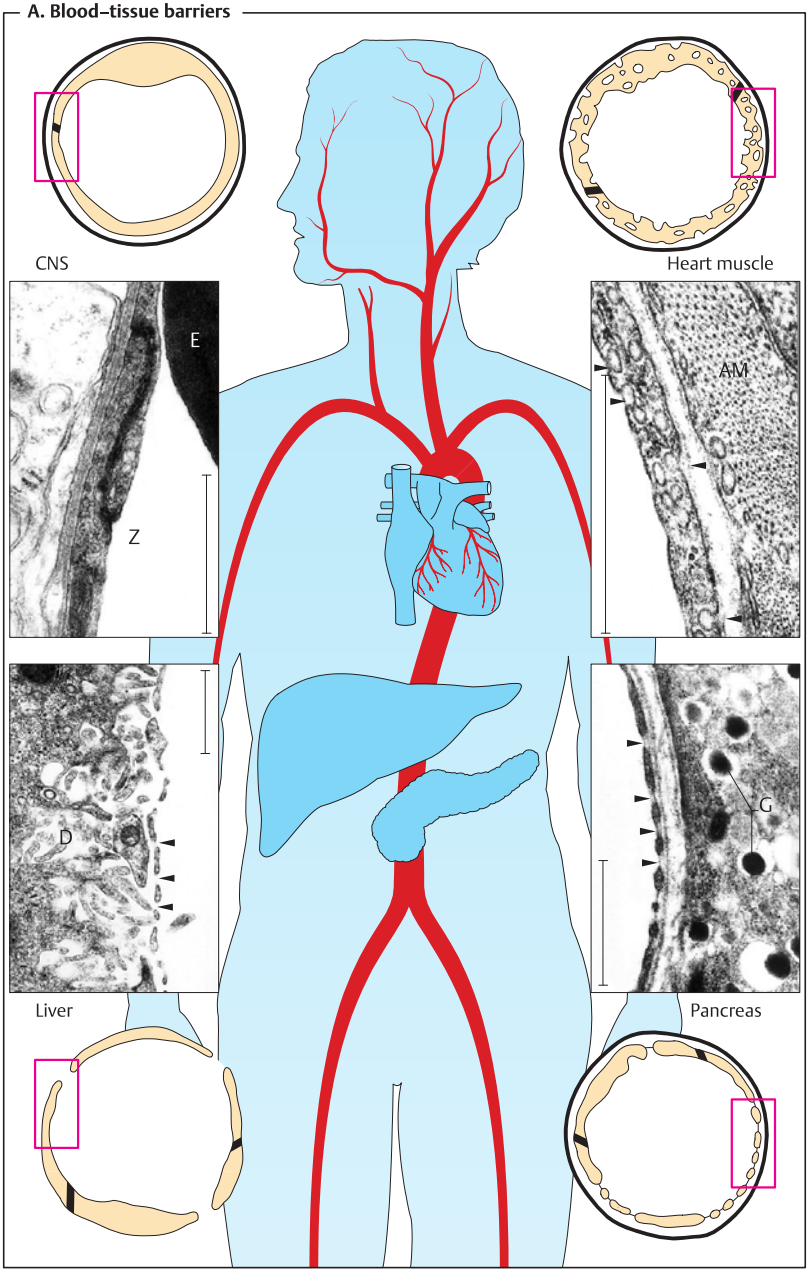

A. Blood–tissue barriers
CNS
Heart muscle
E
Z
AM
D
G
Liver
Pancreas

Fig. 5.2

Membrane Permeation

The ability to penetrate lipid bilayers is a prerequisite for the absorption of drugs, their entry into cells or cellular organelles, and passage across the blood–brain and placental barriers. Owing to their amphiphilic nature, phospholipids form bilayers possessing a hydrophilic surface and a hydrophobic interior (p. 36). Substances may traverse this membrane in three different ways.

► **Diffusion** (► **Fig. 5.3A**). Depending on how lipophilic they are, substances can diffuse directly through the lipid bilayer down the concentration gradient across the membrane (red dots). However, the membrane represents an almost insuperable barrier for highly hydrophilic substances (e.g., norepinephrine).

► **Passive transport** (► **Fig. 5.3A**). Many tissues possess transport systems to enable substances that cannot pass through the membrane to enter the cells and cell compartments where they are required. These transport systems are located in the membranes and are more or less specific for a particular group of substances. No energy is required for passive transport across the membrane. Channels or carrier proteins enable hydrophilic substances to pass through membranes. Examples include voltage- or ligand-controlled ion channels (p. 150), e.g., voltage-gated Na^+ channels and Ca^{2+} channels (p. 204), and aquaporins. **Aquaporins** (p. 176) are specialized transport proteins that enable water to pass through the hydrophobic cell membrane in numerous tissues of the body.

► **Active transport** (► **Fig. 5.3A**). Numerous transport processes in the body use energy in the form of ATP directly or indirectly. This applies particularly when the substances to be transported have to be transported through the cell membrane against a concentration gradient, i.e., "uphill." **Primary active transport** involves proteins that can themselves hydrolyze ATP (ATPase) and thus transport substances. Na^+/K^+-ATPase or H^+/K^+-ATPase in the gastric parietal cells are examples. Some primary active transport proteins act as targets for drugs: digitalis glycosides inhibit Na^+/K^+-ATPases (p. 148). Proton pump inhibitors reduce acid production in the stomach by inhibiting H^+/K^+-ATPase (p. 184).

Secondary active transport processes require functional coupling of a cotransporter to a primary ATP-dependent transporter (► Fig. 5.3**A**). In this case, the energy needed for the transport of the substance is obtained from a downhill shift of ions. The Na^+ gradient (► Fig. 5.3**A**, yellow triangles) is usually the energy donor. To maintain this ion gradient, a Na^+/K^+-ATPase may in turn be responsible. Many neurotransmitter and anion or cation transporters use cellular Na^+ gradients as an energy source (see SLC transporters, p. 44).

► **Transcytosis (vesicular transport,** ► **Fig. 5.3B**). When new vesicles are pinched off, substances dissolved in the extracellular fluid are engulfed and then ferried through the cytoplasm, unless the vesicles (phagosomes) undergo fusion with lysosomes to form phagolysosomes and the transported substance is metabolized.

► **Receptor-mediated endocytosis** (► **Fig. 5.3B**). The drug first binds to membrane surface receptors (**1**, **2**) whose cytosolic domains contact special proteins (adaptins, **3**). Drug-receptor complexes migrate laterally in the membrane and aggregate with other complexes by a clathrin-dependent process to form coated pits (**4**). The affected membrane region invaginates and eventually pinches off to form a detached vesicle (**5**). The clathrin and adaptin coats are shed (**6**), resulting in formation of the "early" endosome (**7**). Inside this, proton concentration rises and causes the drug-receptor complex to dissociate. Next, the receptor-bearing membrane portions separate from the endosome (**8**). These membrane sections recirculate to the plasmalemma (**9**), while the endosome is delivered to the target organelles (**10**).

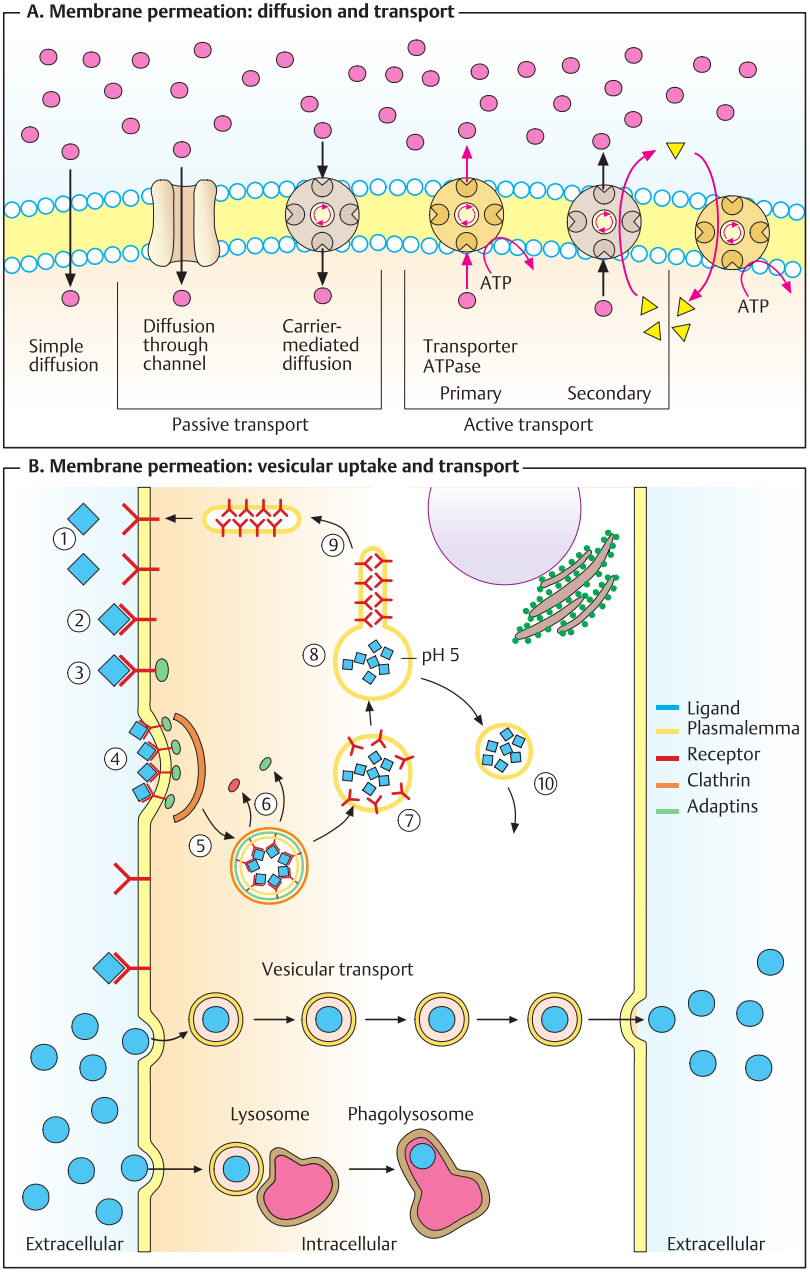

A. Membrane permeation: diffusion and transport
Simple diffusion
Diffusion through channel
Carrier-mediated diffusion
ATP
ATP
Transporter ATPase
Primary
Secondary
Passive transport
Active transport
B. Membrane permeation: vesicular uptake and transport
pH 5
Ligand
Plasmalemma
Receptor
Clathrin
Adaptins
Vesicular transport
Lysosome
Phagolysosome
Extracellular
Intracellular
Extracellular

Fig. 5.3

Drug Transporters

Only a few molecules can pass cell membranes without the aid of specialized proteins for transportation. At least 5% of all human genes code for proteins involved in transport. These transport proteins are very important in pharmacology, as they are involved in the distribution, action, and elimination of drugs.

The **ABC transporter** family (▶ Fig. 5.4**A**) mediates active transport of substances from the interior of functionally polarized cells into the extracellular space ("**efflux transporters**"). These transport proteins contain "**A**TP-**b**inding **c**assettes," which are protein domains that use ATP as an energy carrier for the transport process. The first member of this protein family to be discovered was P-glycoprotein (abbreviations: P-gp, MDR1, ABC B1), which can transport cytostatic agents out of cultured tumor cells, thus rendering the tumor cells less sensitive to the cytostatic effect (p. 302). However, P-glycoprotein and other members of this family are expressed not only in tumor cells but also throughout the body (▶ Fig. 5.4**C**). In the brush border of the intestinal epithelia, for instance, it ensures elimination of drugs and reduces the bioavailability of digoxin. In the luminal side of the endothelial cells of the brain capillaries P-glycoprotein can transport drugs (e.g., the opiate-like antidiarrheal agent loperamide, p. 188) into the blood compartment, thereby limiting their access to the brain. In the bile canaliculi of the liver (see p. 50) and in the apical tubular membranes of the kidney, P-glycoprotein and other "multidrug resistance proteins" (MRP2, -3) promote the elimination of drugs and conjugates. Numerous **drug interactions** occur due to modulation of P-glycoprotein and ABC transporters. Inhibitors of P-glycoprotein such as itraconazole or atorvastatin can increase the bioavailability of the transported drugs. Inducers such as rifampicin or St. John's wort induce expression of P-glycoprotein and other biotransformation proteins, e.g., CYP450 enzymes (p. 54) and glucuronyl transferases (p. 56).

Various transport processes are mediated by **SLC** ("solute carrier") transport proteins (▶ Fig. 5.4**B**). These proteins transport their substrates either by facilitated diffusion or by secondary active processes, exploiting the substance gradients generated by ATPases. For instance, the Na^+/Ca^{2+} exchangers in the heart can use the Na^+ gradient built up by the Na^+/K^+-ATPase for outward transport of Ca^{2+} (see p. 146). SLCs are strongly involved in the permeation of drugs and their metabolites through polarized cells (▶ Fig. 5.4**C**). Moreover, these carriers are also sites of drug action; for example, in neurons, antidepressants inhibit serotonin and/or norepinephrine transport carriers, which belong to the SLC family.

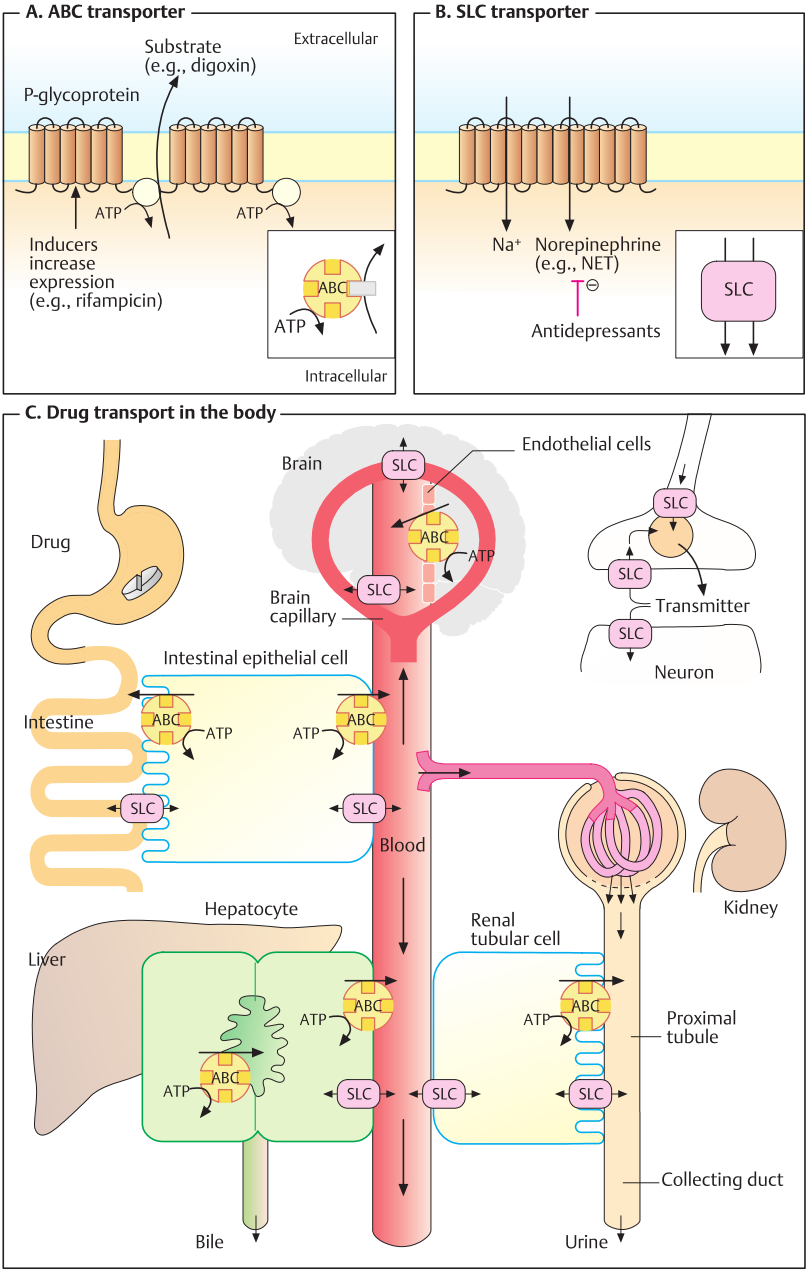

A. ABC transporter
Extracellular
Substrate
(e.g., digoxin)
P-glycoprotein
ATP
ATP
Inducers
increase
expression
(e.g., rifampicin)
ABC
ATP
Intracellular
B. SLC transporter
Na+
Norepinephrine
(e.g., NET)
Antidepressants
SLC
C. Drug transport in the body
Drug
Brain
SLC
Endothelial cells
ABC
ATP
SLC
Brain
capillary
SLC
SLC
Transmitter
SLC
Neuron
Intestinal epithelial cell
Intestine
ABC
ATP
ATP
ABC
SLC
SLC
Blood
Kidney
Hepatocyte
Liver
Renal
tubular cell
ABC
ATP
ATP
ABC
ABC
ATP
Proximal
tubule
SLC
SLC
SLC
Collecting duct
Bile
Urine

Fig. 5.4

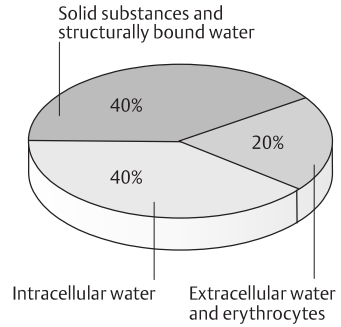
Possible Modes of Drug Distribution

Following its uptake into the body, the drug is distributed (▶ Fig. 5.6A) in the blood (**1**) and through it to the various tissues of the body. Distribution may be restricted to the extracellular space (plasma volume plus interstitial space) (**2**) or may also extend into the intracellular space (**3**). Certain drugs may bind strongly to tissue structures so that plasma concentrations fall significantly even before elimination has begun (**4**).

After being distributed in blood, macromolecular substances remain largely confined to the vascular space, because their permeation through the blood–tissue barrier, or endothelium, is impeded, even where capillaries are fenestrated. This property is exploited therapeutically when loss of blood necessitates refilling of the vascular bed, for instance by infusion of dextran solutions (p. 168). The vascular space is, moreover, predominantly occupied by substances bound with high affinity to plasma proteins (p. 48; determination of the plasma volume with protein-bound dyes). Unbound, free drug may leave the bloodstream, albeit with varying ease, because the blood–tissue barrier (p. 40) is differently developed in different segments of the vascular tree. These regional differences are not illustrated in ▶ Fig. 5.6.

Distribution in the body is determined by the ability to penetrate membranous barriers. Hydrophilic substances (e.g., inulin) are neither taken up into cells nor bound to cell surface structures and can thus be used to determine the extracellular fluid volume (**2**). Lipophilic substances diffuse through the cell membrane and, as a result, achieve a uniform distribution in body fluids (**3**).

Body weight may be broken down as illustrated in the pie-chart (▶ Fig. 5.5). Further subdivisions are shown in ▶ Fig. 5.6.



Potential aqueous space for dissolved drugs.

Fig. 5.5

The volume ratio of interstitial: intracellular water varies with age and body weight. On a percentage basis, interstitial fluid volume is large in premature or normal neonates (up to 50% of body water), and smaller in the obese and the aged.

The concentration (c) of a solution corresponds to the amount (D) of substance dissolved in a volume (V); thus, $c = D/V$. If the dose of drug (D) and its plasma concentration (c) are known, a volume of distribution (V) can be calculated from $V = D/c$. However, this represents an *apparent* (notional) volume of distribution (V_{app}), because an even distribution in the body is assumed in its calculation. Homogeneous distribution will not occur if drugs are bound to cell membranes (**5**) or to membranes of intracellular organelles (**6**) or are stored within organelles (**7**). In these cases, plasma concentration c becomes small and V_{app} can exceed the actual size of the available fluid volume. Conversely, if a major fraction of drug molecules is bound to plasma proteins, c becomes large and the calculated value for V_{app} may then be smaller than that attained biologically.

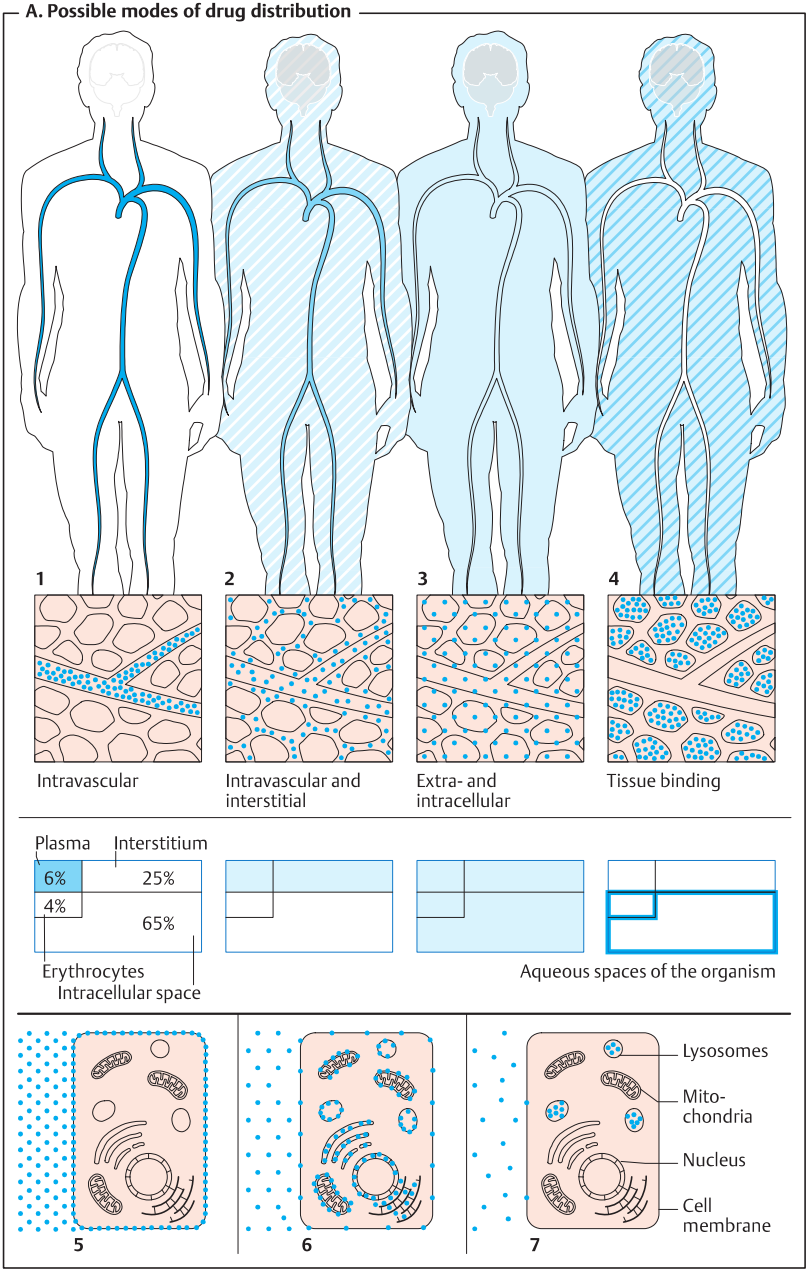

A. Possible modes of drug distribution
1
2
3
4
Intravascular
Intravascular and interstitial
Extra- and intracellular
Tissue binding
Plasma
Interstitium
6%
25%
4%
65%
Erythrocytes
Intracellular space
Aqueous spaces of the organism
5
6
7
Lysosomes
Mito-chondria
Nucleus
Cell membrane

Fig. 5.6

Binding of Drugs to Plasma Proteins

Having entered the blood, drugs may bind to the protein molecules that are present in abundance, resulting in the formation of drug–protein complexes.

Protein binding involves primarily albumin and, to a lesser extent, β-globulins and acidic glycoproteins. Other plasma proteins (e.g., transcortin, transferrin, thyroxine-binding globulin) serve specialized functions in connection with specific substances. The degree of binding is governed by the concentration of the reactants and the affinity of a drug for a given protein. Albumin concentration in plasma amounts to 4.6 g/100 mL, or 0.6 mM, and thus provides a very high binding capacity (two sites per molecule). As a rule, drugs exhibit much lower affinity (K_D ~10^{-5}–10^{-3}M) for plasma proteins than for their specific binding sites (receptors). In the range of therapeutically relevant concentrations, protein binding of most drugs increases linearly with concentration (exceptions: salicylate and certain sulfonamides).

The albumin molecule has different binding sites for anionic and cationic ligands, but *van der Waals* forces also contribute (p. 76). The extent of binding correlates with drug hydrophobicity (repulsion of drug by water).

Binding to plasma proteins is instantaneous and reversible, i.e., any change in the concentration of unbound drug is immediately followed by a corresponding change in the concentration of bound drug. Protein binding is of great importance because it is the concentration of free drug that determines the intensity of the effect. At a given total plasma concentration (e.g., 100 ng/ml) the *effective* concentration will be 90 ng/mL for a drug 10% bound to protein, but 1 ng/mL for a drug 99% bound to protein. The reduction in concentration of free drug resulting from protein binding affects not only the intensity of the effect but also biotransformation (e.g., in the liver) and elimination from the kidney, because only free drug will enter hepatic sites of metabolism or undergo glomerular filtration. When concentrations of free drug fall, drug is resupplied from binding sites on plasma proteins. Binding to plasma protein is equivalent to a depot in prolonging the duration of the effect by retarding elimination, whereas the intensity of the effect is reduced. If two substances have affinity for the same binding site on the albumin molecule, they may compete for that site. One drug may displace another from its binding site and thereby elevate the free (effective) concentration of the displaced drug (a form of **drug interaction**). Elevation of the free concentration of the displaced drug means increased effectiveness and accelerated elimination.

A decrease in the concentration of albumin (in liver disease, nephrotic syndrome, poor general condition) leads to altered pharmacokinetics of drugs that are highly bound to albumin.

Plasma protein-bound drugs that are substrates for transport carriers can be cleared from blood at high velocity; e.g., *p*-aminohippurate by the renal tubule and sulfobromophthalein by the liver. Clearance rates of these substances can be used to determine renal or hepatic blood flow.

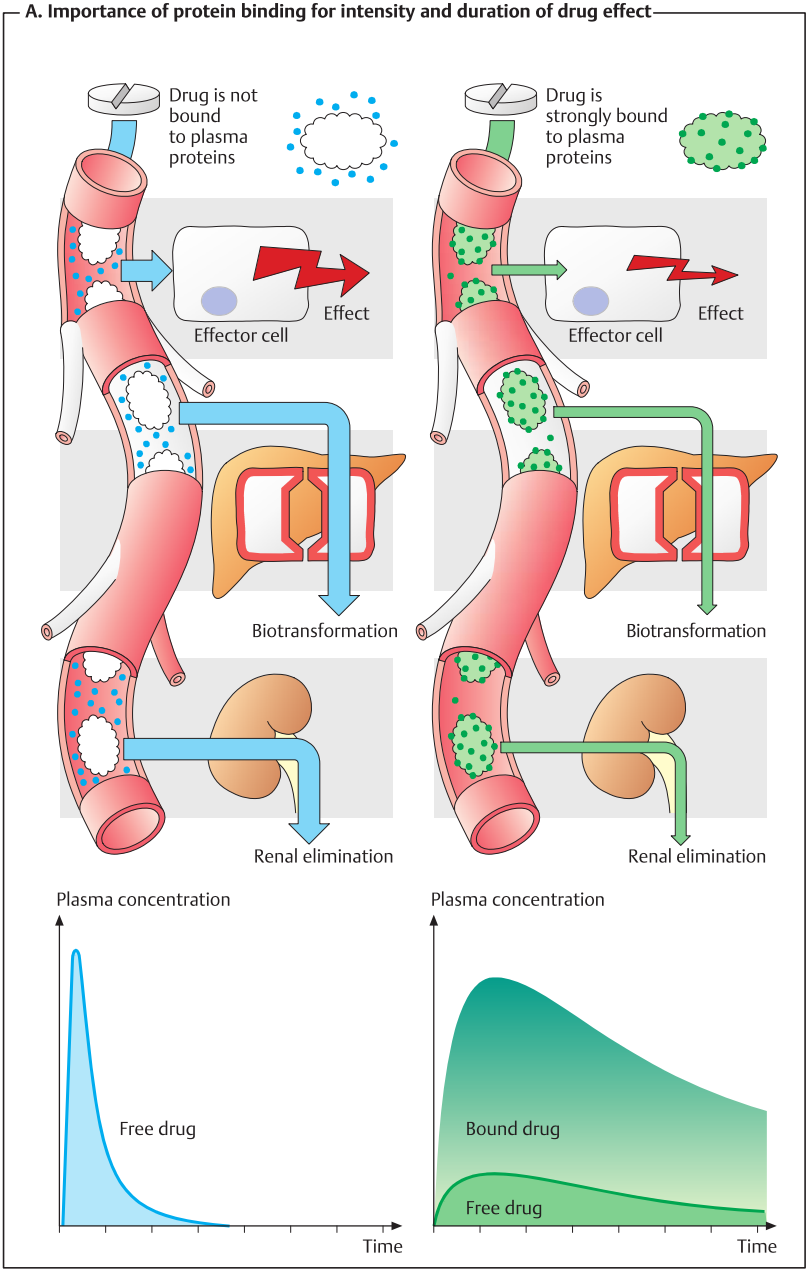

A. Importance of protein binding for intensity and duration of drug effect
Drug is not bound to plasma proteins
Effector cell
Effect
Biotransformation
Renal elimination
Drug is strongly bound to plasma proteins
Effector cell
Effect
Biotransformation
Renal elimination
Plasma concentration
Free drug
Time
Plasma concentration
Bound drug
Free drug
Time

Fig. 5.7

The Liver as an Excretory Organ

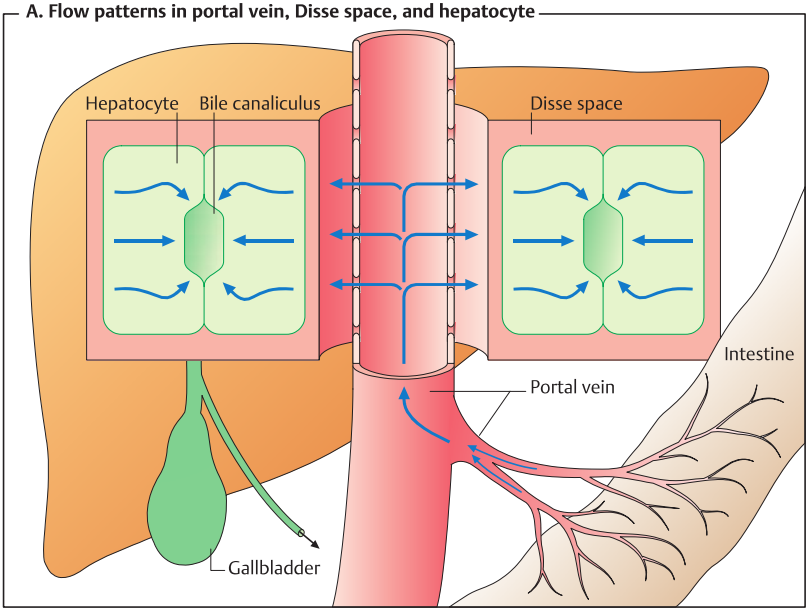
As the major organ of drug biotransformation, the liver is richly supplied with blood, of which 1100 mL is received each minute from the intestines through the portal vein and 350 ml through the hepatic artery, comprising nearly ⅓ of cardiac output. The blood content of hepatic vessels and sinusoids amounts to 500 mL. Owing to the widening of the portal lumen, intrahepatic blood flow decelerates (▶ Fig. 6.1**A**). Moreover, the endothelial lining of hepatic sinusoids (p. 40) contains pores large enough to permit rapid exit of plasma proteins. Thus, blood and hepatic parenchyma are able to maintain intimate contact and intensive exchange of substances, which is further facilitated by microvilli covering the hepatocyte surfaces abutting Disse spaces.

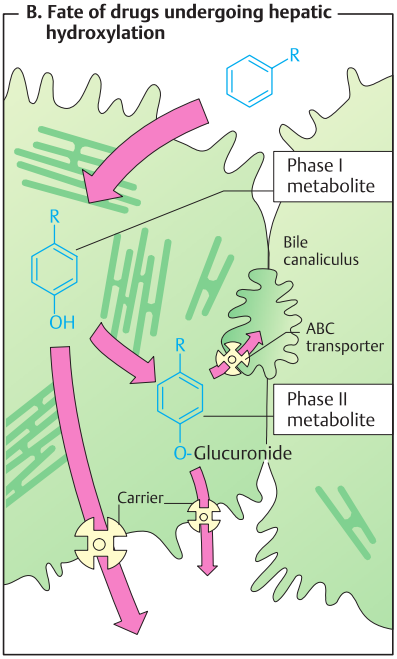
The hepatocyte secretes biliary fluid into the bile canaliculi (dark green), tubular intercellular clefts that are sealed off from the blood spaces by tight junctions. Secretory activity in the hepatocytes results in movement of fluid toward the canalicular space (▶ Fig. 6.1**A**).

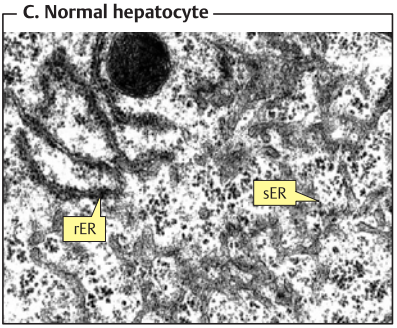
The hepatocyte is endowed with numerous metabolically important enzymes that are localized in part in mitochondria and in part on membranes of the *rough* (rER) and *smooth* (sER) *endoplasmic reticulum.* Enzymes of the sER play a most important role in drug biotransformation. At this site, direct consumption of molecular oxygen (O_2) takes place in oxidative reactions. Because these enzymes can catalyze either hydroxylation or oxidative cleavage of –N–C– or –O–C– bonds, they are referred to as *"mixed-function" oxidases or hydroxylases.* The integral component of this enzyme system is the iron-containing cytochrome P450 (p. 54). Many P450 isozymes are known and they exhibit different patterns of substrate specificity. Interindividual genetic differences in isozyme make-up (e.g., CYP2D6) underlie subject-to-subject variations in drug biotransformation. The same holds for other enzyme systems; hence, the phenomenon is generally referred to as *genetic polymorphism of biotransformation.*

Compared with hydrophilic drugs not undergoing transport, lipophilic drugs are more rapidly taken up from the blood into hepatocytes and more readily gain access to mixed-function oxidases embedded in sER membranes. For instance, a drug having lipophilicity by virtue of an aromatic substituent (phenyl ring) (▶ Fig. 6.1**B**) can be hydroxylated and thus become more hydrophilic, in what is known as a phase I reaction (p. 52). Besides oxidases, sER also contains reductases and glucuronyl transferases. The latter conjugate glucuronic acid with hydroxyl, carboxyl, amine, and amide groups and hence also phenolic products of phase I metabolism (phase II conjugation). Phase I and phase II metabolites can be transported back into the blood—probably via a gradient-dependent carrier—or actively secreted into bile via the ABC transporter (ATP-binding cassette transporter). Different transport proteins are available: for instance, MRP2 (the multidrug resistance-associated protein 2) transports anionic conjugates into the bile canaliculi, whereas MRP3 can route these via the basolateral membrane of the hepatocyte toward the general circulation.

Prolonged exposure to substrates of one of the membrane-bound enzymes results in a proliferation of sER membranes in the liver (cf. ▶ Fig. 6.1**C** and ▶ Fig. 6.1**D**). The molecular mechanism of this sER "hypertrophy" has been elucidated for some drugs: thus, phenobarbital binds to a nuclear receptor (constitutive androstane receptor) that regulates the expression of cytochromes CYP2C9 and CYP2D6. Enzyme induction leads to accelerated biotransformation, not only of the inducing agent but also of other drugs (a form of **drug interaction**). With continued exposure, it develops in a few days, resulting in an increase in reaction velocity, maximally 2–3-fold, that disappears after removal of the inducing agent.


A. Flow patterns in portal vein, Disse space, and hepatocyte
Hepatocyte
Bile canaliculus
Disse space
Intestine
Portal vein
Gallbladder


B. Fate of drugs undergoing hepatic hydroxylation
R
Phase I metabolite
R
OH
Bile canaliculus
ABC transporter
R
Phase II metabolite
O-Glucuronide
Carrier


C. Normal hepatocyte
sER
rER

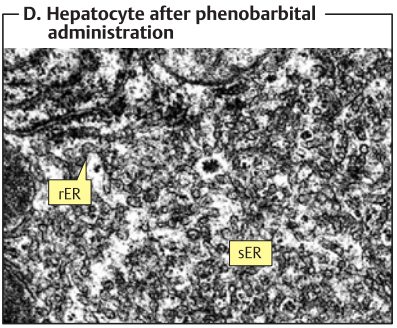

D. Hepatocyte after phenobarbital administration
rER
sER

Fig. 6.1

Biotransformation of Drugs

Many drugs undergo chemical modification in the body (**biotransformation**). Most often this process entails a loss of biological activity and an increase in hydrophilicity (water solubility), thereby promoting elimination via the renal and hepatic route.

Hydrolytic cleavages, along with *oxidations, reductions, alkylations,* and *dealkylations,* constitute **phase I reactions** of drug metabolism. These reactions subsume all metabolic processes apt to alter drug molecules chemically and take place chiefly in the liver. In **phase II (synthetic) reactions**, *conjugation products* of either the drug itself or its phase I metabolites are formed, for instance, with glucuronic or sulfuric acid (p. 56).

Oxidation reactions (▶ Fig. 6.2**A**) can be divided into two kinds: those in which oxygen is incorporated into the drug molecule, and those in which primary oxidation causes part of the molecule to be lost. The former include **hydroxylations**, **epoxidations**, and **sulfoxidations**. Hydroxylations may involve alkyl substituents or aromatic ring systems (e.g., propranolol). In both cases, products are formed that are conjugated to an organic acid residue, e.g., glucuronic acid, in a subsequent phase II reaction.

Hydroxylation may also take place at nitrogens, resulting in hydroxylamines (e.g., acetaminophen).

The second type of oxidative biotransformation comprises **dealkylations**. In the case of primary or secondary amines, dealkylation of an alkyl group starts at the carbon adjacent to the nitrogen; in the case of tertiary amines, with hydroxylation of the nitrogen (e.g., lidocaine). The intermediary products are labile and break up into the dealkylated amine and aldehyde of the alkyl group removed. O-dealkylation and S-dearylation proceed via an analogous mechanism (e.g., phenacetin and azathioprine, respectively).

Reduction reactions (▶ Fig. 6.2**B**) may occur at oxygen or nitrogen atoms. Keto oxygens are converted into a hydroxyl group, as in the reduction of the prodrugs cortisone and prednisone to the active glucocorticoids cortisol and prednisolone, respectively. N-reductions occur in azo or nitro compounds (e.g., nitrazepam). Nitro groups can be reduced to amine groups via nitroso and hydroxylamino intermediates.

▶ **Hydrolysis (▶ Fig. 6.2C).** The special case of the endogenous transmitter acetylcholine illustrates well the high speed of ester hydrolysis. Acetylcholine is broken down so rapidly by specific acetylcholinesterase (p. 120) and nonspecific serum cholinesterase that it cannot be used therapeutically.

Ester hydrolysis does not invariably lead to inactive metabolites, as exemplified by acetylsalicylic acid. The cleavage product, salicylic acid, retains pharmacological activity. In certain cases, drugs are administered in the form of esters in order to facilitate uptake into the body (enalapril—enalaprilate, testosterone—decanoate-testosterone). In these cases, the ester itself is not active but its hydrolytic product is. Thus, an inactive precursor or prodrug is administered, and formation of the active molecule occurs only after hydrolysis in the blood.

Peptidases are also important in pharmacology as they produce highly reactive cleavage products, for example, fibrin (p. 164), or highly active oligopeptides such as angiotensin II (p. 142), bradykinin, and enkephalins (p. 210) from biologically inactive peptides. Peptidases exhibit some substrate selectivity and can be selectively inhibited, as exemplified by the formation of angiotensin II, whose actions include vasoconstriction. Angiotensin II is formed from angiotensin I by cleavage of the C-terminal amino acids leucine and histidine. Hydrolysis is catalyzed by "angiotensin-converting enzyme" (ACE). Peptide analogues such as captopril or enalapril block this enzyme.

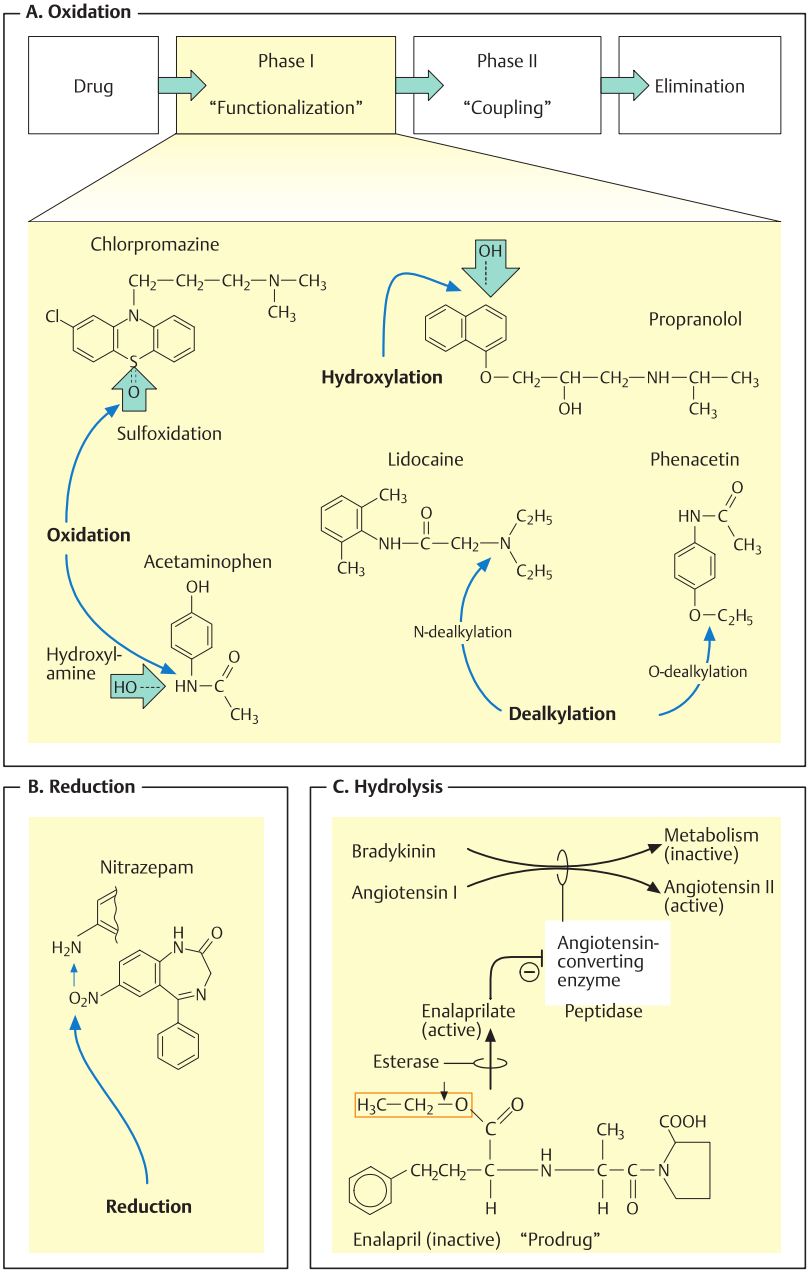

A. Oxidation
Drug
Phase I
"Functionalization"
Phase II
"Coupling"
Elimination
Chlorpromazine
Sulfoxidation
Hydroxylation
Propranolol
Oxidation
Acetaminophen
Hydroxyl-
amine
Lidocaine
N-dealkylation
Phenacetin
O-dealkylation
Dealkylation
B. Reduction
Nitrazepam
Reduction
C. Hydrolysis
Bradykinin
Angiotensin I
Metabolism
(inactive)
Angiotensin II
(active)
Angiotensin-
converting
enzyme
Peptidase
Enalaprilate
(active)
Esterase
Enalapril (inactive)
"Prodrug"

Fig. 6.2

Drug Metabolism by Cytochrome P450

► **Cytochrome P450 enzyme.** Drug metabolism can be divided into two phases: Phase I reactions and phase II reactions (p. 52). A major part of phase I reactions is catalyzed by hemoproteins, the so-called cytochrome P450 (CYP) enzymes (► Fig. 6.3**A**). To date about 40 genes for cytochrome P450 proteins have been identified in humans; among these, the protein families CYP1, CYP2, and CYP3 are important in drug metabolism (► Fig. 6.3**B**). The bulk of CYP enzymes are located in the liver and the intestinal wall, which explains why these organs are responsible for the major part of drug metabolism.

► **Substrates, inhibitors, and inducers.** Cytochromes are enzymes with broad substrate specificities. Accordingly, pharmaceuticals of diverse chemical structure can be metabolized by a given enzyme protein. When several drugs are metabolized by the same isozyme, clinically important interactions may result. In these, **substrates** (drugs metabolized by CYP) can be distinguished from **inhibitors** (drugs that are bound to CYP with high affinity, interfere with the breakdown of substrates, and are themselves metabolized slowly) (► Fig. 6.3**A**). The amount of hepatic CYP enzymes is a major determinant of metabolic capacity. An increase in enzyme concentration usually leads to accelerated drug metabolism. Numerous endogenous and exogenous substances, such as drugs, can augment the expression of CYP enzymes and thus act as **CYP inducers** (p. 68). Many of these inducers activate specific transcription factors in the nucleus of hepatocytes, leading to activation of mRNA synthesis and subsequent production of CYP isozyme protein. Some inducers also increase the expression of P-glycoprotein transporters; as a result, enhanced metabolism by CYP and increased membrane transport by P-glycoprotein can act in concert to render a drug ineffective.

The table in ► Fig. 6.3**B** provides an overview of different CYP isozymes along with their substrates, inhibitors, and inducers. Obviously, when a patient is to be exposed to polypharmaceutic regimens (especially multimorbid subjects), it would be imprudent to start therapy without checking whether the drugs being contemplated include CYP inducers or inhibitors, some of which may dramatically alter pharmacokinetics.

► **Drug interaction due to CYP induction or inhibition.** Life-threatening interactions have been observed in patients taking inducers of CYP3A4 isozyme during treatment with ciclosporin for the prevention of kidney and heart transplant rejection. Rifampicin (rifampin) and also St. John's wort preparations (available without prescription) may increase expression of CYP3A4 to such an extent as to lower plasma levels of ciclosporin below the therapeutic range (► Fig. 6.3**C**). As immunosuppression becomes inadequate, the risk of transplant rejection will be enhanced. In the presence of rifampicin, other drugs that are substrates of CYP3A4 may become ineffective. For this reason, the use of rifampicin is contraindicated in HIV patients being treated with protease inhibitors. As a rule, inhibitors of CYP enzymes elevate plasma levels of drugs that are substrates of the same CYP enzymes; in this manner, they raise the risk of undesirable toxic effects. The antifungal agent itraconazole enhances the nephrotoxicity of ciclosporin by such a mechanism (► Fig. 6.3**C**).

► **Increase in drug effect due to CYP inhibition.** Cobicistat is an inhibitor of CYP3A enzymes (and of various drug transporters), which can be given to inhibit biotransformation of elvitegravir, an HIV integrase inhibitor (p. 288) and thus increase its effect. Cobicistat acts as a "pharmacokinetic booster" and has no intrinsic pharmacodynamic effect.

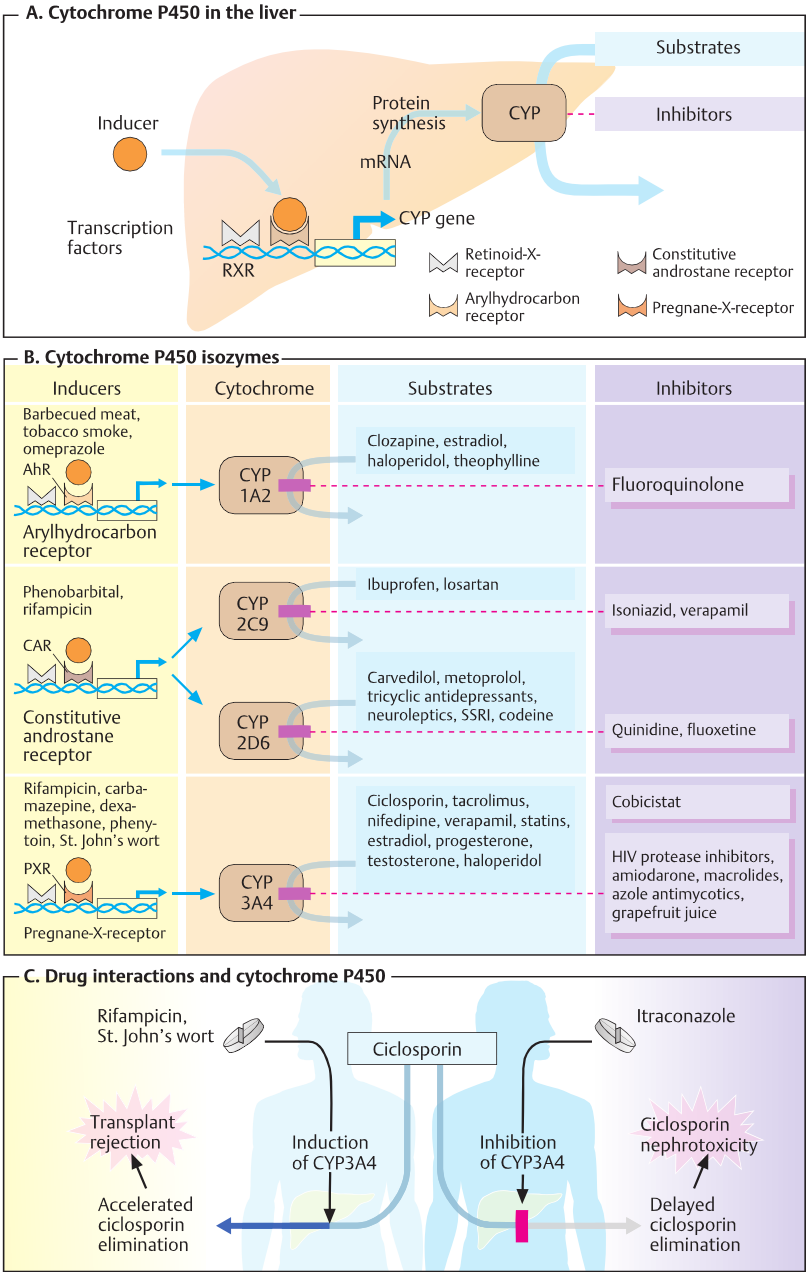

A. Cytochrome P450 in the liver
Substrates
Inhibitors
Inducer
Protein synthesis
CYP
mRNA
Transcription factors
CYP gene
RXR
Retinoid-X-receptor
Constitutive androstane receptor
Arylhydrocarbon receptor
Pregnane-X-receptor
B. Cytochrome P450 isozymes
Inducers
Cytochrome
Substrates
Inhibitors
Barbecued meat, tobacco smoke, omeprazole
AhR
Arylhydrocarbon receptor
CYP 1A2
Clozapine, estradiol, haloperidol, theophylline
Fluoroquinolone
Phenobarbital, rifampicin
CAR
Constitutive androstane receptor
CYP 2C9
Ibuprofen, losartan
Isoniazid, verapamil
CYP 2D6
Carvedilol, metoprolol, tricyclic antidepressants, neuroleptics, SSRI, codeine
Quinidine, fluoxetine
Rifampicin, carbamazepine, dexamethasone, phenytoin, St. John's wort
PXR
Pregnane-X-receptor
CYP 3A4
Ciclosporin, tacrolimus, nifedipine, verapamil, statins, estradiol, progesterone, testosterone, haloperidol
Cobicistat
HIV protease inhibitors, amiodarone, macrolides, azole antimycotics, grapefruit juice
C. Drug interactions and cytochrome P450
Rifampicin, St. John's wort
Ciclosporin
Itraconazole
Transplant rejection
Induction of CYP3A4
Inhibition of CYP3A4
Ciclosporin nephrotoxicity
Accelerated ciclosporin elimination
Delayed ciclosporin elimination

Fig. 6.3

Enterohepatic Circulation

Drugs administered orally (▶ Fig. 6.4**A**1) and absorbed from the intestine (▶ Fig. 6.4**A**2) reach the liver via the portal vein, where they may be conjugated with glucuronic acid (▶ Fig. 6.4**B**, salicylic acid), with sulfuric acid (▶ Fig. 6.4**B**, the deacylated form of the laxative bisacodyl), or with other polar molecules (3). The hydrophilic conjugates can pass from the hepatocyte into the bile by means of transport mechanisms (4) so that they are returned to the intestine; that is, they are eliminated in the bile (5). The hydrophilic conjugation products cannot cross the intestinal epithelium. However, *O*-glucuronides can be cleaved by the β-glucuronidases of colon bacteria (6) and the released substances can be **reabsorbed**. This gives rise to an **enterohepatic circulation**, which would appear to trap the drug in the body. However, the conjugated products exit the liver cells not only into the bile but also into the blood (7). Glucuronides with a molecular weight <300 pass mainly into the blood, while glucuronides with a molecular weight >300 pass into the bile to a greater extent. The glucuronides secreted into the blood from the liver cells undergo glomerular filtration in the kidney but, because of their hydrophilicity, they are not reabsorbed like the original substance but are excreted in the urine (8).

Drugs that undergo enterohepatic circulation are thus excreted slowly. The drugs that undergo enterohepatic circulation include digitoxin and nonsteroidal anti-inflammatory agents.

Conjugation Reactions

The most important conjugation reactions (▶ Fig. 6.4**B**) or phase II reactions consist of conjugation of a drug or its metabolite to glucuronic acid. At the pH of body fluids, the carboxyl group of glucuronic acid is almost completely dissociated, and the negative charge gives a glucuronidated molecule high polarity and thus low membrane penetrability.

The conjugation reaction does not take place spontaneously but only when the glucuronic acid is present in its activated form, that is, bound to uridine diphosphate. Microsomal glucuronyl transferases transfer glucuronic acid from this complex to the acceptor molecule. If the acceptor molecule is a phenol or an alcohol, a glucuronide ether is produced, but if it is transferred to a carboxyl group, the result is a glucuronide ester. In both cases, these are *O*-glucuronides. *N*-Glucuronides can be formed with amines, which, unlike *O*-glucuronides, cannot be cleaved by bacterial β-glucuronidases.

Sulfotransferases dissolved in the cytoplasm transfer activated sulfuric acid (3′-phosphoadenine-5′-phosphosulfate) to alcohols and phenols. As in the case of the glucuronides, the conjugation product is an acid.

This differs from the conjugation product formed from activated acetic acid (acetyl coenzyme A) with the mediation of an acyl transferase and an alcohol or phenol. This conjugation product is not acid in character.

Acyl transferases are involved in the transfer of the amino acids glycine and glutamine to carboxyl acids. In these cases, an amide bond is formed between the carboxyl group of the acceptor molecule and the amino group of the transferred amino acid. The acid function of glycine or glutamine remains free in the conjugation product.

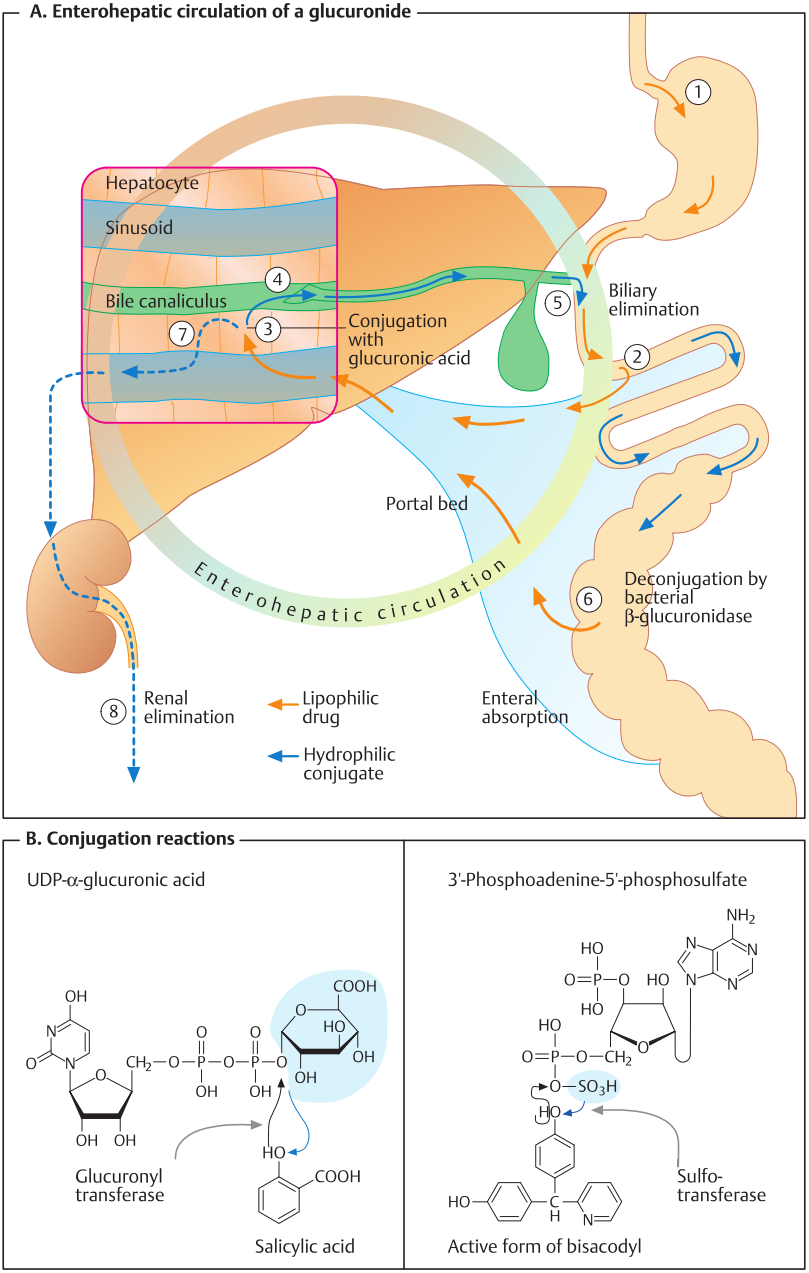

A. Enterohepatic circulation of a glucuronide
Hepatocyte
Sinusoid
Bile canaliculus
Conjugation with glucuronic acid
Biliary elimination
Portal bed
Enterohepatic circulation
Deconjugation by bacterial β-glucuronidase
Renal elimination
Lipophilic drug
Hydrophilic conjugate
Enteral absorption
B. Conjugation reactions
UDP-α-glucuronic acid
Glucuronyl transferase
Salicylic acid
3'-Phosphoadenine-5'-phosphosulfate
Sulfo-transferase
Active form of bisacodyl

Fig. 6.4

The Kidney as an Excretory Organ

Most drugs are eliminated in urine either chemically unchanged or as metabolites. The kidney permits elimination because the vascular wall structure in the region of the glomerular capillaries (▶ Fig. 6.5**A**,**B**) allows unimpeded passage into urine of blood solutes having molecular weights (MW) < 5000. Filtration is restricted at MW < 50 000 and ceases at MW > 70 000. With few exceptions, therapeutically used drugs and their metabolites have much smaller molecular weights and can therefore undergo **glomerular filtration**, i.e., pass from blood into primary urine. Separating the **capillary endothelium** from the **tubular epithelium**, the **basal membrane** contains negatively charged macromolecules and acts as a filtration barrier for high-molecular-weight substances. The relative density of this barrier depends on the electric charge of molecules that attempt to permeate it. In addition, the diaphragmatic slits between podocyte processes play a part in glomerular filtration.

Apart from **glomerular filtration** (▶ Fig. 6.5**B**), drugs present in blood may pass into urine by **active secretion** (▶ Fig. 6.5**C**). Certain cations and anions are secreted by the epithelium of the proximal tubules into the tubular fluid via special energy-consuming transport systems. These transport systems have a limited capacity. When several substrates are present simultaneously, competition for the carrier may occur.

During passage down the renal tubule, primary urinary volume shrinks to about 1%; accordingly, there is a corresponding concentration of filtered drug or drug metabolites (▶ Fig. 6.5**A**). The resulting concentration gradient between urine and interstitial fluid is preserved in the case of drugs incapable of permeating the tubular epithelium. However, with lipophilic drugs the concentration gradient will favor **reabsorption** of the filtered molecules. In this case, reabsorption is not based on an active process but results instead from passive diffusion. Accordingly, for protonated substances, the extent of reabsorption is dependent upon urinary pH or the degree of dissociation. The degree of dissociation varies as a function of the urinary pH and the pK_a, which represents the pH value at which half of the substance exists in protonated (or unprotonated) form. This relationship is illustrated graphically (▶ Fig. 6.5**D**) with the example of a protonated amine having a pK_a of 7. In this case, at urinary pH 7, 50% of the amine will be present in the protonated, hydrophilic, membrane-impermeant form (blue dots), whereas the other half, representing the uncharged amine (red dots), can leave the tubular lumen in accordance with the resulting concentration gradient. If the pK_a of an amine is higher (pK_a = 7.5) or lower (pK_a = 6.5), a correspondingly smaller or larger proportion of the amine will be present in the uncharged, reabsorbable form. Lowering or raising urinary pH by half a pH unit would result in analogous changes.

The same considerations hold for acidic molecules, with the important difference that alkalinization of the urine (increased pH) will promote the deprotonization of -COOH groups and thus impede reabsorption. Intentional alteration of urinary pH can be used in intoxications with proton-acceptor substances in order to hasten elimination of the toxin (e.g., alkalinization → phenobarbital; acidification → methamphetamine).

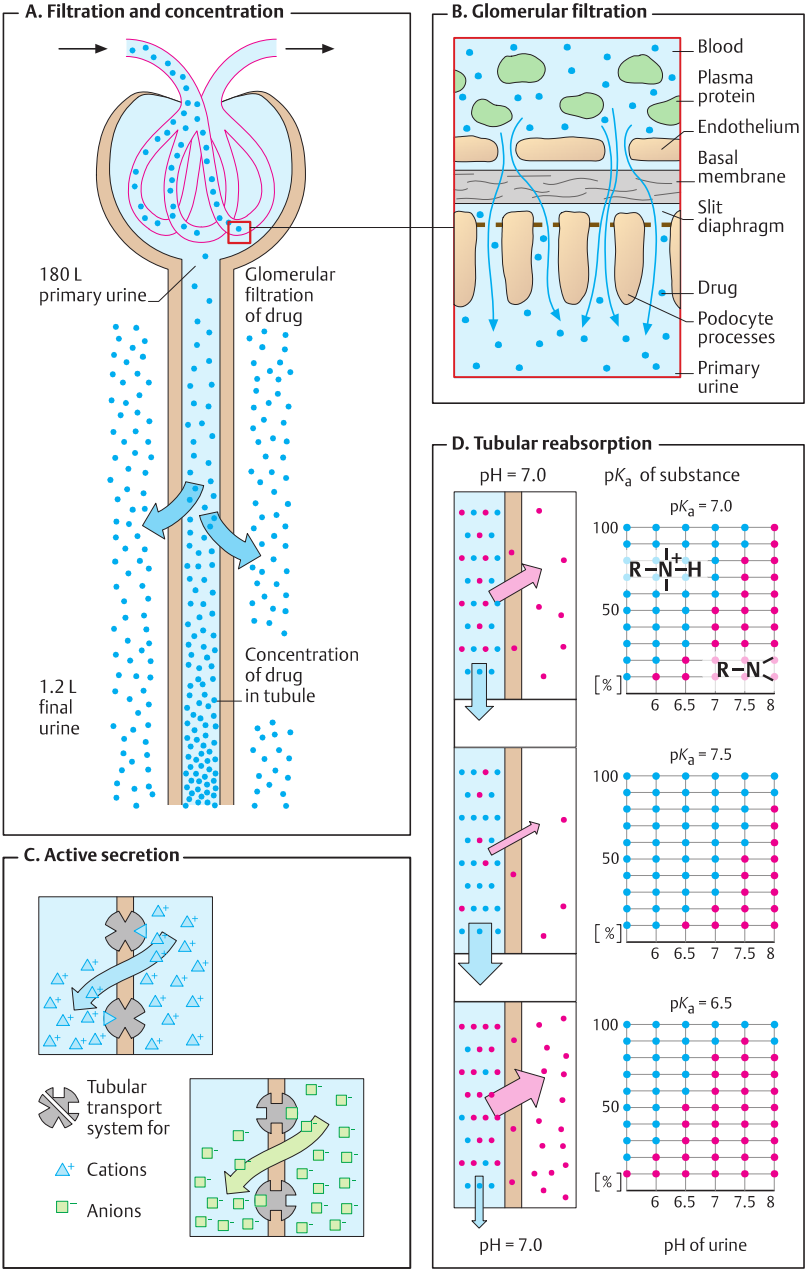

A. Filtration and concentration
180 L primary urine
Glomerular filtration of drug
Concentration of drug in tubule
1.2 L final urine
B. Glomerular filtration
Blood
Plasma protein
Endothelium
Basal membrane
Slit diaphragm
Drug
Podocyte processes
Primary urine
C. Active secretion
Tubular transport system for
Cations
Anions
D. Tubular reabsorption
pH = 7.0
pKa of substance
pKa = 7.0
pKa = 7.5
pKa = 6.5
100
50
[%]
6 6.5 7 7.5 8
pH = 7.0
pH of urine

Fig. 6.5

Presystemic Elimination

The morphological barriers of the body are illustrated on pp. 38–41. Depending on the physicochemical properties of drugs, intended targets on the surface or the inside of cells, or of bacterial organisms, may be reached to varying degrees or not at all. Whenever a drug cannot be applied locally but must be given by the systemic route, its pharmacokinetics will be subject to yet another process. This becomes very obvious if we follow the route of an orally administered drug from its site of absorption to the general circulation. Any of the following may occur:

1. The drug permeates through the epithelial barrier of the gut into the enterocyte; however, a **P-glycoprotein** transports it back into the intestinal lumen. As a result, the amount actually absorbed can be greatly diminished. This counter-transport can vary interindividually for an identical substance and moreover may be altered by other drugs.
2. En route from the intestinal lumen to the general circulation, the ingested substance is broken down enzymatically, e.g., by **cytochrome P450 oxidases**.
   a) Degradation may start already in the intestinal mucosa. Other drugs or agents may inhibit or stimulate the activity of enteral cytochrome oxidases. A peculiar example is grapefruit juice, which inhibits CYP3A4 oxidase in the gut wall and thereby causes blood concentrations of other important drugs to rise to toxic levels.
   b) Metabolism in the liver, through which the drug must pass, plays the biggest role. Here, many enzymes are at work to alter endogenous and exogenous substances chemically so as to promote their elimination. Examples of different metabolic reactions are presented in the section "Biotransformation of drugs" (p. 52). Depending on the quantity of drug being taken up and metabolized by the hepatocytes, only a fraction of the amount absorbed may reach the blood in the hepatic vein. Importantly, an increase in enzyme activity (increase in smooth endoplasmic reticulum) can be induced by other drugs.

   The processes referred to in 2a and b above are subsumed under the term "**presystemic elimination**."
3. **Parenteral administration** of a drug of course circumvents presystemic elimination. After i.v., s.c., or i.m. injection, the drug travels via the vena cava, the right heart ventricle, and the lungs to the left ventricle and, thence, to the systemic circulation and the coronary system. As a lipid-rich organ with a large surface, the lungs can take up lipophilic or amphiphilic agents to a considerable extent and release them slowly after blood levels fall again. During fast delivery of drug, the lungs act as a buffer and protect the heart against excessive concentrations after rapid i.v. injection.

In certain therapeutic situations, rapid presystemic elimination may be desirable. An important example is the use of glucocorticoids in the **treatment of asthma**. Because a significant portion of inhaled drug is swallowed, glucocorticoids with complete presystemic elimination entail only a minimal systemic load for the organism (p. 356). The use of clopidogrel for inhibition of platelet aggregation provides an example of a desirable presystemic activation (p. 166).

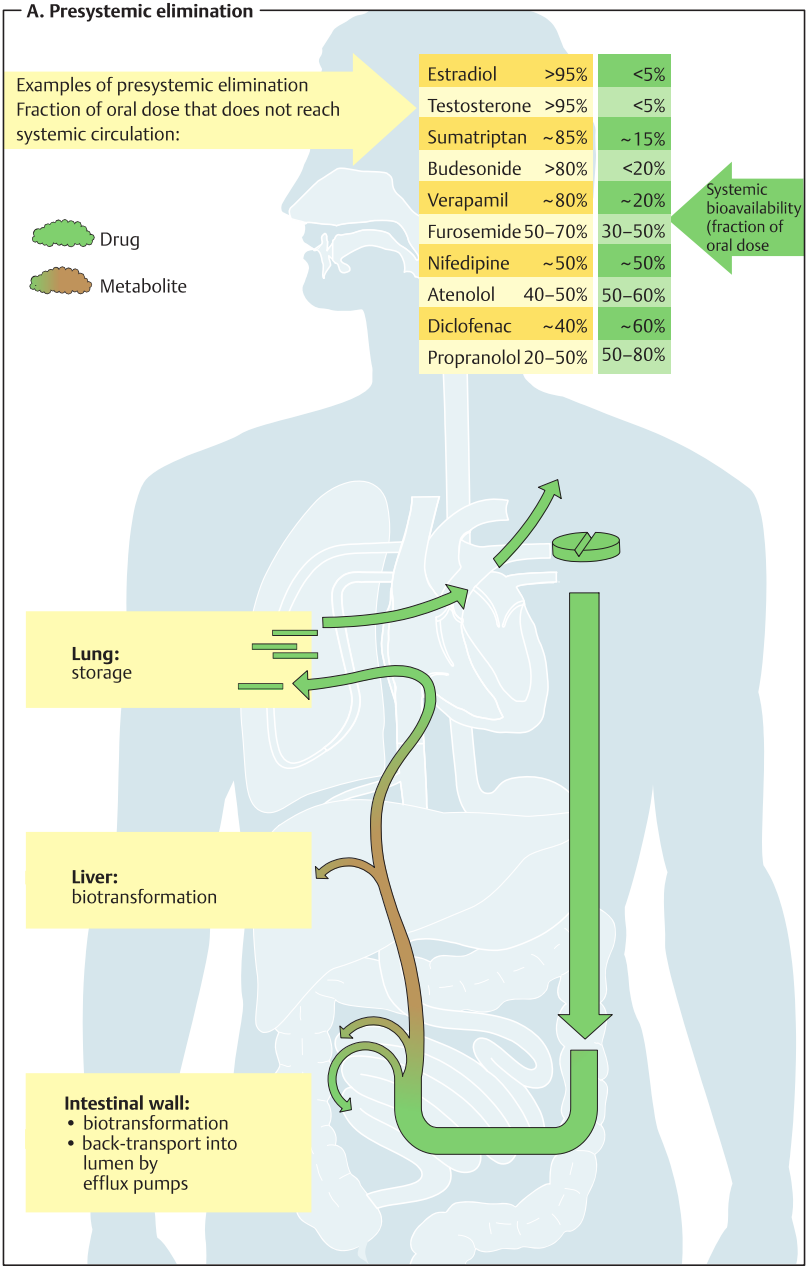

A. Presystemic elimination
Examples of presystemic elimination
Fraction of oral dose that does not reach systemic circulation:
Estradiol >95% <5%
Testosterone >95% <5%
Sumatriptan ~85% ~15%
Budesonide >80% <20%
Verapamil ~80% ~20%
Furosemide 50–70% 30–50%
Nifedipine ~50% ~50%
Atenolol 40–50% 50–60%
Diclofenac ~40% ~60%
Propranolol 20–50% 50–80%
Systemic bioavailability (fraction of oral dose
Drug
Metabolite
Lung:
storage
Liver:
biotransformation
Intestinal wall:
• biotransformation
• back-transport into lumen by efflux pumps

Fig. 6.6

Drug Concentration in the Body as a Function of Time—First Order (Exponential) Rate Processes

Processes such as drug absorption and elimination display exponential characteristics. For absorption, this follows from the simple fact that the amount of drug being moved per unit of time depends on the concentration difference (gradient) between two body compartments (Fick's law). In drug absorption from the alimentary tract, the intestinal content and blood would represent the compartments containing initially high and low concentrations, respectively. In drug elimination via the kidney, excretion often depends on glomerular filtration, i.e., the filtered amount of drug present in primary urine. As the blood concentration falls, the amount of drug filtered per unit of time diminishes. The resulting exponential decline is illustrated in ▶ Fig. 7.1**A**. The exponential time course implies constancy of the interval during which the concentration decreases by one-half. This interval represents the half-life ($t_{1/2}$) and is related to the elimination rate constant k by the equation $t_{1/2} = (\ln 2)/k$. The two parameters, together with the initial concentration c_0, describe a first-order (exponential) rate process.

The constancy of the process permits calculation of the plasma volume that would be cleared of drug, if the remaining drug were not to assume a homogeneous distribution in the total volume (a condition not met in reality). The **notional plasma volume freed of drug per unit of time** is termed the **clearance**. Depending on whether plasma concentration falls as a result of urinary excretion or of metabolic alteration, clearance is considered to be renal or hepatic. Renal and hepatic clearances add up to total clearance (Cl_{tot}) in the case of drugs that are eliminated unchanged via the kidney and biotransformed in the liver. Cl_{tot} represents the sum of all processes contributing to elimination; it is related to the half-life ($t_{1/2}$) and the apparent volume of distribution V_{app} (p. 46) by the equation:

$$t_{1/2} = \ln 2 \times \frac{V_{app}}{Cl_{tot}} \qquad (7.1)$$

The smaller the volume of distribution or the larger the total clearance, the shorter is the half-life.

In the case of drugs renally eliminated in unchanged form, the half-life of elimination can be calculated from the cumulative excretion in urine; the final total amount eliminated corresponds to the amount absorbed.

Hepatic elimination obeys exponential kinetics because metabolizing enzymes operate in the quasi-linear region of their concentration–activity curve, and hence the amount of drug metabolized per unit time diminishes with decreasing blood concentration.

The best-known exception to exponential kinetics is the elimination of alcohol (ethanol), which obeys a *linear* time course (zero-order kinetics), at least at blood concentrations >0.02%. It does so because the rate-limiting enzyme, alcohol dehydrogenase, achieves half-saturation at very low substrate concentrations, i.e., at about 80 mg/L (0.008%). Thus, reaction velocity reaches a plateau at blood ethanol concentrations of about 0.02%, and the amount of drug eliminated per unit time remains constant at concentrations above this level.

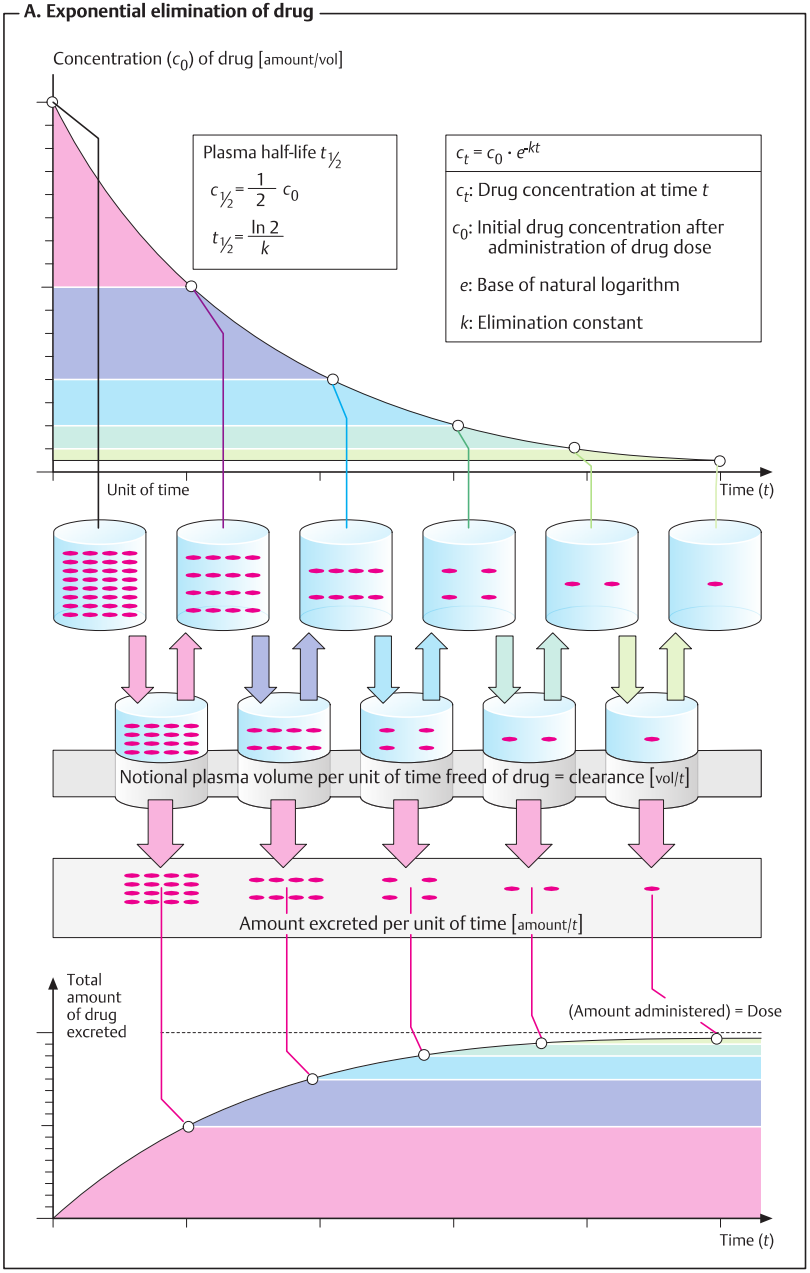

A. Exponential elimination of drug
Concentration (c_0) of drug [amount/vol]
Plasma half-life $t_{1/2}$
$c_{1/2} = \frac{1}{2} c_0$
$t_{1/2} = \frac{\ln 2}{k}$
$c_t = c_0 \cdot e^{kt}$
c_t: Drug concentration at time t
c_0: Initial drug concentration after administration of drug dose
e: Base of natural logarithm
k: Elimination constant
Unit of time
Time (t)
Notional plasma volume per unit of time freed of drug = clearance [vol/t]
Amount excreted per unit of time [amount/t]
Total amount of drug excreted
(Amount administered) = Dose
Time (t)

Fig. 7.1

Time Course of Drug Concentration in Plasma

▶ **Time course of drug concentration (▶ Fig. 7.2A).** Drugs are taken up into and eliminated from the body by various routes. The body thus represents an open system wherein the actual drug concentration reflects the interplay of intake (ingestion) and egress (elimination). When orally administered drug is absorbed from the stomach and intestine, speed of uptake depends on many factors, including the speed of drug dissolution (in the case of solid dosage forms) and of gastrointestinal transit; the membrane penetrability of the drug; its concentration gradient across the mucosa–blood barrier; and mucosal blood flow. **Absorption** from the intestine causes the drug concentration in blood to increase. Transport in blood conveys the drug to different organs (**distribution**), into which it is taken up to a degree compatible with its chemical properties and rate of blood flow through the organ. For instance, well-perfused organs such as the brain receive a greater proportion than do less well-perfused ones. Uptake into tissue causes the blood concentration to fall. Absorption from the gut diminishes as the mucosa–blood gradient decreases. Plasma concentration reaches a peak when the amount of drug leaving the blood per unit of time equals that being absorbed.

Drug entry into hepatic and renal tissue constitutes movement into the **organs of elimination**. The characteristic phasic time course of drug concentration in plasma represents the sum of the constituent processes of **absorption**, **distribution**, and **elimination**, which overlap in time. When distribution takes place significantly faster than elimination, there is an initial rapid and then a greatly retarded fall in the plasma level, the former being designated the α-phase (distribution phase), the latter the β-phase (elimination phase). When the drug is distributed faster than it is absorbed, the time course of the plasma level can be described in mathematically simplified form by the Bateman function (k_1 and k_2 represent the rate constants for absorption and elimination, respectively).

▶ **Application and time course of drug concentration (▶ Fig. 7.2B).** The velocity of absorption depends on the route of administration. The more rapid the absorption, the shorter will be the time (t_{max}) required to reach the peak plasma level (c_{max}), the higher will be the c_{max}, and the earlier will the plasma level begin to fall again.

The *area under the plasma level–time curve* (AUC) is independent of the route of administration, provided the doses and bioavailability are the same (law of corresponding areas). The AUC can thus be used to determine the **bioavailability *F*** of a drug. The ratio of AUC values determined after oral and intravenous administrations of a given dose of a particular drug corresponds to the proportion of drug entering the systemic circulation after oral administration. Thus,

$$F = \frac{AUC\ oral\ administration}{AUC\ i.v.\ administration} \qquad (7.2)$$

The determination of plasma levels affords a comparison of different proprietary preparations containing the same drug in the same dosage. Identical plasma level–time curves of different manufacturers' products with reference to a standard preparation indicate **bioequivalence** with the standard of the preparation under investigation.

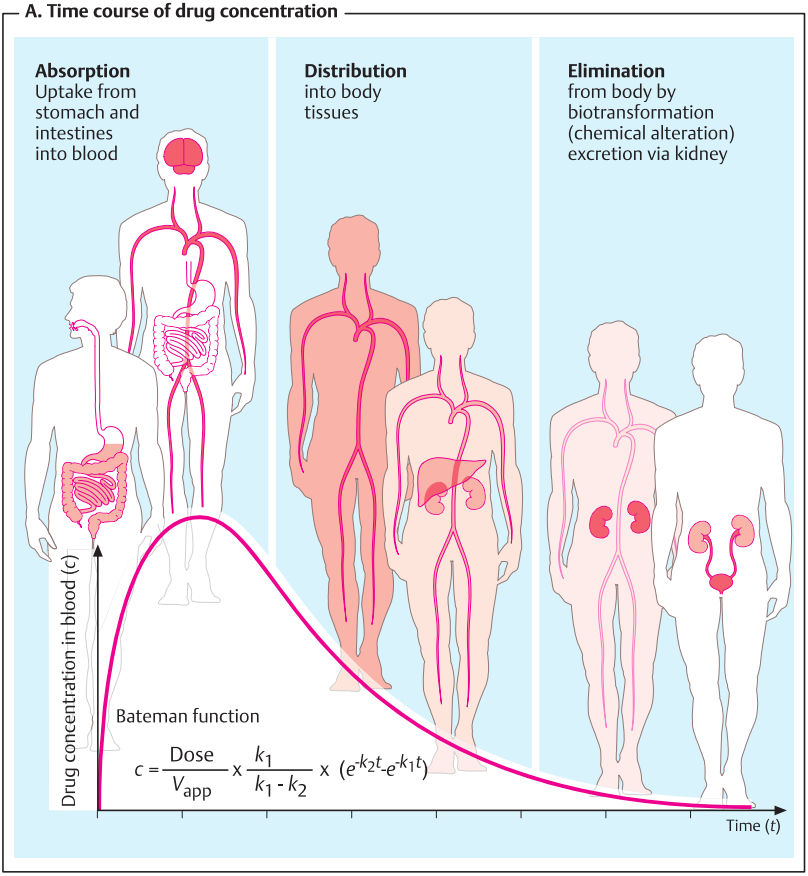

A. Time course of drug concentration
Absorption
Uptake from stomach and intestines into blood
Distribution
into body tissues
Elimination
from body by biotransformation (chemical alteration) excretion via kidney
Drug concentration in blood (c)
Bateman function
c = Dose / V_app x k1 / (k1 - k2) x (e^-k2t - e^-k1t)
Time (t)
B. Route of administration and time course of drug concentration
Drug concentration in blood (c)
Intravenous
Intramuscular
Subcutaneous
Oral
Time (t)

Fig. 7.2

Time Course of Drug Plasma Levels during Repeated Dosing

When a drug is administered at regular intervals over a prolonged period (▶ Fig. 7.3**A**), the rise and fall of drug concentration in blood will be determined by the relationship between the half-life of elimination and the time interval between doses. If the amount of drug administered in each dose has been eliminated before the next dose is given, repeated intake at constant intervals will result in similar plasma levels. If intake occurs before the preceding dose is eliminated completely, the next dose will add to the residual amount still present in the body, i.e., the drug **accumulates**. The shorter the dosing interval relative to the elimination half-life, the larger will be the residual amount of drug to which the next dose is added and the more extensively will the drug accumulate in the body. However, at a given dosing frequency, the drug does not accumulate infinitely and a **steady state** concentration (c_{ss}) or **accumulation equilibrium** is eventually reached. This is so because the activity of elimination processes is concentration-dependent. The higher the drug concentration rises, the greater is the amount eliminated per unit of time. After several doses, the concentration will have climbed to a level at which the amounts eliminated and taken in per unit of time become equal, i.e., a steady state is reached. Within this concentration range, the plasma level will continue to rise (peak) and fall (trough) as dosing is continued at regular intervals. The height of the steady state (c_{ss}) depends upon the amount (D) administered per dosing interval (τ) and the clearance (Cl):

$$c_{ss} = \frac{D}{\tau \times Cl} \qquad (7.3)$$

The speed at which the steady state is reached corresponds to the speed of elimination of the drug. The time needed to reach 90% of the concentration plateau is about 3 times the $t_{1/2}$ of elimination.

Time Course of Drug Plasma Levels during Irregular Intake

In practice, it proves difficult to achieve a plasma level that undulates evenly around the desired effective concentration. For instance, if two successive doses are omitted ("?" in ▶ Fig. 7.3**B**), the plasma level will drop below the therapeutic range and a longer period will be required to regain the desired plasma level. In everyday life, patients will be apt to neglect to take drugs at the scheduled time. **Patient compliance** means strict adherence to the prescribed regimen. Apart from poor compliance, the same problem may occur when the total daily dose is divided into three individual doses (t.i.d.) and the first dose is taken at breakfast, the second at lunch, and the third at supper. Under these conditions, the nocturnal dosing interval will be twice the diurnal one. Consequently, plasma levels during the early morning hours may have fallen far below the desired, or possibly urgently needed, range.

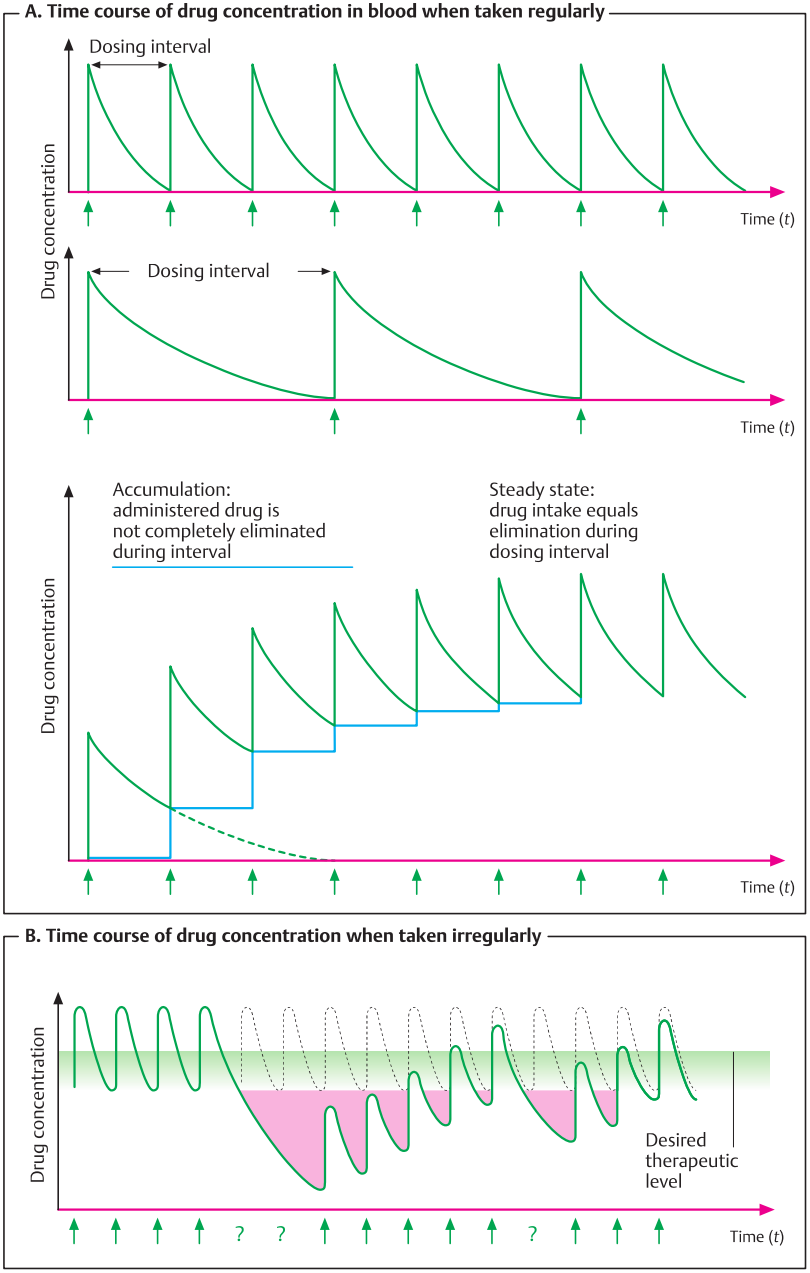

A. Time course of drug concentration in blood when taken regularly
Dosing interval
Drug concentration
Time (t)
Dosing interval
Time (t)
Accumulation:
administered drug is
not completely eliminated
during interval
Steady state:
drug intake equals
elimination during
dosing interval
Drug concentration
Time (t)
B. Time course of drug concentration when taken irregularly
Drug concentration
Desired
therapeutic
level
? ? ?
Time (t)

Fig. 7.3

Accumulation: Dose, Dose Interval, and Plasma Level Fluctuation

Successful drug therapy in many illnesses is accomplished only if the drug concentration is maintained at a steady high level (▶ Fig. 7.4**A**). This requirement necessitates regular drug intake and a dosage schedule that ensures that the plasma concentration neither falls below the therapeutically effective range nor exceeds the minimal toxic concentration. A constant plasma level would, however, be undesirable if it accelerated a loss of effectiveness (development of tolerance), or if the drug were required to be present at specified times only.

A steady plasma level can be achieved by giving the drug in a constant intravenous infusion, the height of the steady state plasma level being determined by the infusion rate. This procedure is routinely used in hospital settings, but is generally impracticable. With oral administration, dividing the total daily dosage into several individual doses, e.g., four, three, or two, offers a practical compromise. When the daily dose is given in several divided doses, the mean plasma level shows little fluctuation.

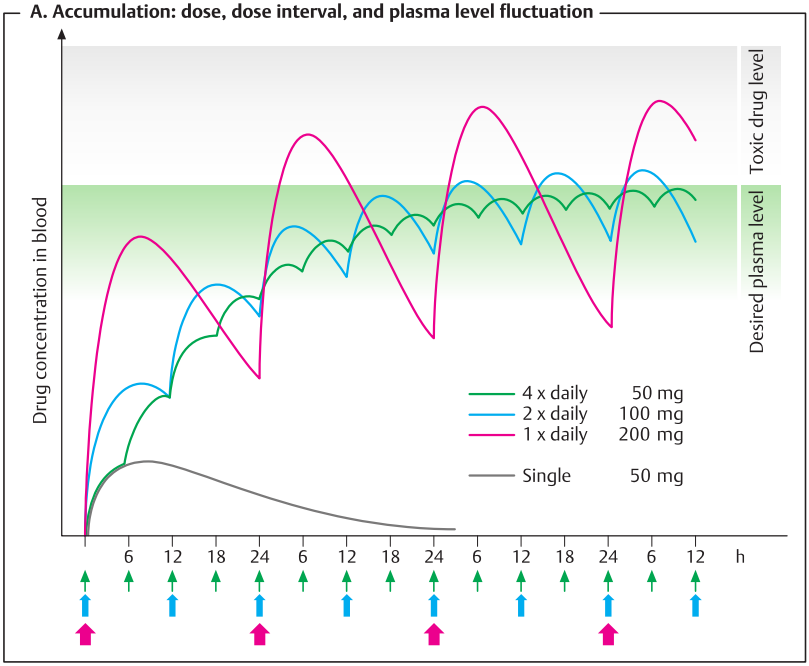
In practice, it is found that a regimen of frequent regular drug ingestion is not well adhered to by patients (unreliability or lack of "compliance" by patients). The degree of fluctuation in plasma level over a given dosing interval can be reduced by a dosage form permitting slow (sustained) release (p. 28).

The time required to reach steady state accumulation during multiple constant dosing depends on the rate of elimination. As a rule of thumb, a plateau is reached after approximately three elimination half-lives ($t_{1/2}$).

For slowly eliminated drugs, which tend to accumulate extensively (phenprocoumon, digitoxin, methadone), the optimal plasma level is attained only after a long period. Here, increasing the initial doses (loading dose) will speed up the attainment of equilibrium, which is subsequently maintained with a lower dose (maintenance dose). For slowly eliminated substances, single daily dosing may suffice to maintain a steady plasma level.

Change in Elimination Characteristics during Drug Therapy

With any drug taken regularly and accumulating to the desired plasma level, it is important to consider that conditions for biotransformation and excretion do not necessarily remain constant (▶ Fig. 7.4**B**). Elimination may be hastened due to enzyme induction (p. 50), e.g., CYP induction (p. 54), or due to a change in urinary pH (p. 58). Consequently, the steady state plasma level declines to a new value corresponding to the new rate of elimination. The drug effect may diminish or disappear. Conversely, when elimination is impaired (e.g., in progressive renal insufficiency), the mean plasma level of renally eliminated drugs rises and may enter a toxic concentration range.


A. Accumulation: dose, dose interval, and plasma level fluctuation
Drug concentration in blood
Toxic drug level
Desired plasma level
4 x daily 50 mg
2 x daily 100 mg
1 x daily 200 mg
Single 50 mg
6 12 18 24 6 12 18 24 6 12 18 24 6 12 h

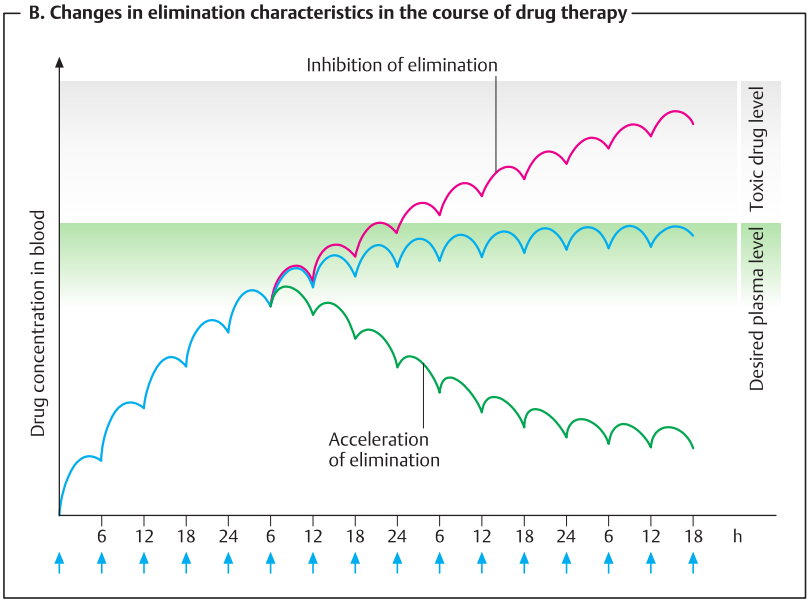

B. Changes in elimination characteristics in the course of drug therapy
Inhibition of elimination
Drug concentration in blood
Toxic drug level
Desired plasma level
Acceleration of elimination
6 12 18 24 6 12 18 24 6 12 18 24 6 12 18 h

Fig. 7.4

Dose–Response Relationship

The effect of a substance depends on the amount administered, i.e., the dose. If the dose chosen is below the critical threshold (subliminal dosing), an effect will be absent. Depending on the nature of the effect to be measured, increasing doses may cause the effect to increase in intensity. Thus, the effect of an antipyretic or hypotensive drug can be quantified in a graded fashion, in that the extent of fall in body temperature or blood pressure is being measured.

The dose–effect relationship may vary depending on the sensitivity of the individual person receiving the drug: i.e., for the same effect, different doses may be required in different individuals. The interindividual variation in sensitivity is especially obvious with effects of the "all-or-none" kind.

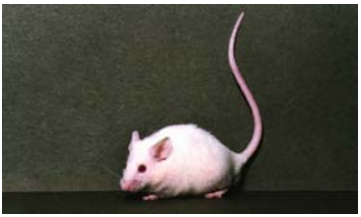
To illustrate this point, we consider an experiment in which the subjects individually respond in all-or-none fashion, as in the Straub tail phenomenon (▶ Fig. 8.1**A**). Mice react to morphine with excitation, evident in the form of an abnormal posture of the tail and limbs. The dose dependence of this phenomenon is observed in groups of animals (e.g., 10 mice per group) injected with increasing doses of morphine. At the low dose only the most sensitive, at increasing doses a growing proportion, and at the highest dose all of the animals are affected (▶ Fig. 8.1**B**). There is a relationship between the frequency of responding animals and the dose given. At 2 mg/kg, 1 out of 10 animals reacts; at 10 mg/kg, 5 out of 10 respond. The **dose–frequency relationship** results from the different sensitivity of individuals, which, as a rule, exhibits a log-normal distribution (▶ Fig. 8.1**C**, graph at right, linear scale). If the cumulative frequency (total number of animals responding at a given dose) is plotted against the logarithm of the dose (abscissa), a *sigmoid* curve results (▶ Fig. 8.1**C**, graph at left, semi-logarithmic scale). The inflection point of the curve lies at the dose at which one half of the group has responded. The dose range encompassing the dose–frequency relationship reflects the variation in individual sensitivity to the drug. Although similar in shape, a dose–frequency relationship has, thus, a meaning different from that of a **dose–effect relationship**. The latter can be evaluated in one individual and results from an intraindividual dependency of the effect on drug concentration.

The evaluation of a dose–effect relationship within a group of human subjects is made more difficult by interindividual differences in sensitivity. To account for the biological variation, measurements have to be carried out on a representative sample and the results averaged. Thus, recommended therapeutic doses will be appropriate for the majority of patients, but not necessarily for each individual.

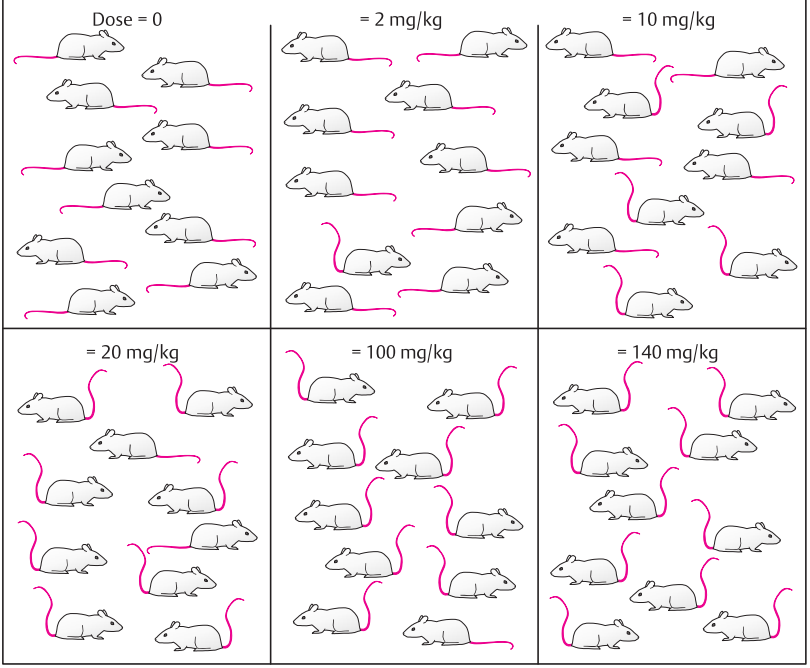
The variation in sensitivity may be based on pharmacokinetic differences (same dose → different plasma levels) or on differences in target organ sensitivity (same plasma level → different effects).

To enhance therapeutic safety, clinical pharmacology has led efforts to discover the causes responsible for interindividual drug responsiveness in patients. This field of research is called *pharmacogenetics*. Often the underlying reason is a difference in enzyme property or activity. Ethnic variations are additionally observed. Prudent physicians will attempt to determine the metabolic status of a patient before prescribing a particular drug.

A. Abnormal posture in mouse given morphine



B. Incidence of effect as a function of dose



C. Dose–frequency relationship

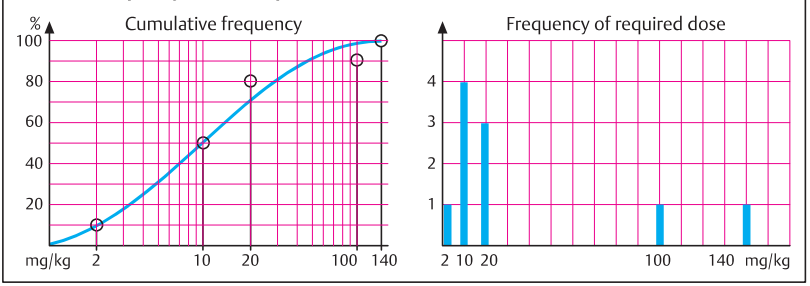


Fig. 8.1

Concentration–Effect Relationship

As a rule, the therapeutic effect or toxic action of a drug depends critically on the response of a single organ or a limited number of organs; for example, blood flow is affected by a change in vascular luminal width (▶ Fig. 8.2**A**). By isolating critical organs or tissues from a larger functional system, these actions can be studied with more accuracy; for instance, vasoconstrictor agents can be examined in isolated preparations from different regions of the vascular tree, e.g., the portal or saphenous veins, or the mesenteric, coronary, or basilar arteries. In many cases, isolated organs or organ parts can be kept viable for hours in an appropriate nutrient medium sufficiently supplied with oxygen and held at a suitable temperature. Responses of the preparation to a physiological or pharmacological stimulus can be determined by a suitable recording apparatus. Thus, narrowing of a blood vessel is recorded with the help of two wire loops by which the vessel is suspended under tension.

Experimentation on isolated organs offers several *advantages:*

1. The drug concentration in the tissue is usually known.
2. Reduced complexity and ease of relating stimulus and effect.
3. It is possible to circumvent compensatory responses that may partially cancel the primary effect in the intact organism; for example, the heart rate-increasing action of norepinephrine cannot be demonstrated in the intact organism because a simultaneous rise in blood pressure elicits a counter regulatory reflex that slows cardiac rate.
4. The ability to examine a drug effect over its full range of intensities; for example, it would be impossible in the intact organism to follow negative chronotropic effects to the point of cardiac arrest.

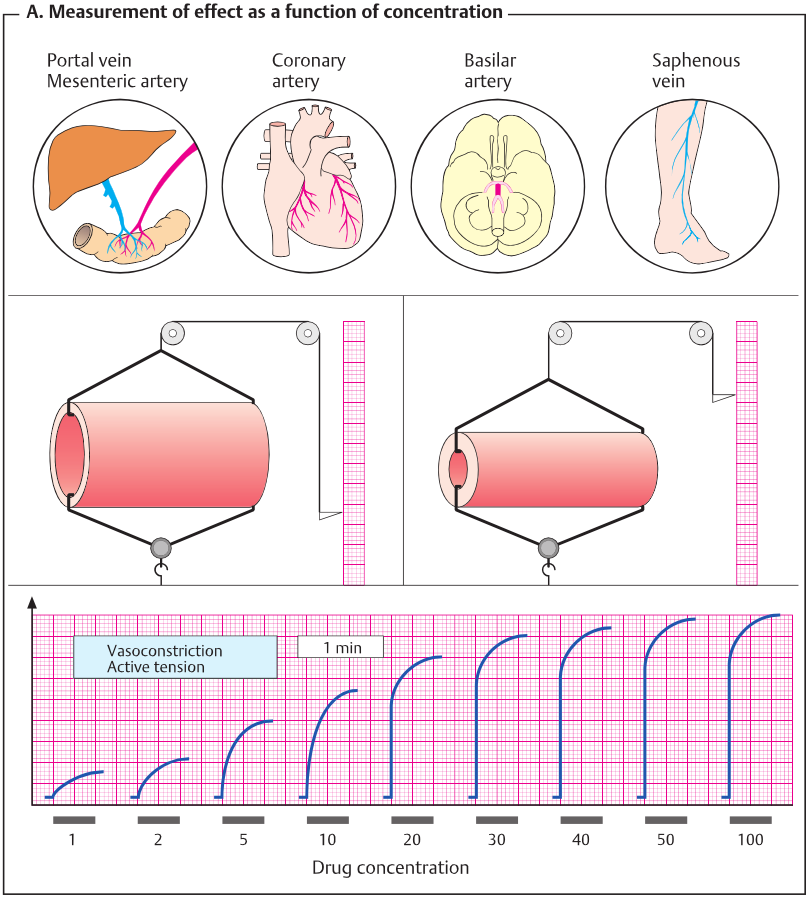
Disadvantages are:

1. Unavoidable tissue injury during dissection.
2. Loss of physiological regulation of function in the isolated tissue.
3. The artificial milieu imposed on the tissue.

These drawbacks are less important if isolated organ systems are used merely for comparing the potency of different substances. The use of isolated cells offers a further simplification of the test system. Thus, quantitation of certain drug effects can be achieved with particular ease in cell cultures. A more marked "reduction" consists in the use of isolated subcellular structures, such as plasma membranes, endoplasmic reticulum, or lysosomes. With increasing reduction, extrapolation to the intact organism becomes more difficult and less certain.

Concentration–Effect Curves

As the concentration is raised by a constant factor, the *increment in effect* diminishes steadily and tends asymptotically toward zero the closer one comes to the maximally effective concentration (▶ Fig. 8.2**B**). The concentration at which a maximal effect occurs cannot be measured accurately; however, that eliciting a half-maximal effect (EC_{50}) is readily determined. This typically corresponds to the inflection point of the concentration–response curve in a semi-logarithmic plot (log concentration on abscissa). Full characterization of a concentration–effect relationship requires determination of the EC_{50}, the maximally possible effect (E_{max}), and the slope at the point of inflection.


A. Measurement of effect as a function of concentration
Portal vein
Mesenteric artery
Coronary artery
Basilar artery
Saphenous vein
Vasoconstriction
Active tension
1 min
1
2
5
10
20
30
40
50
100
Drug concentration

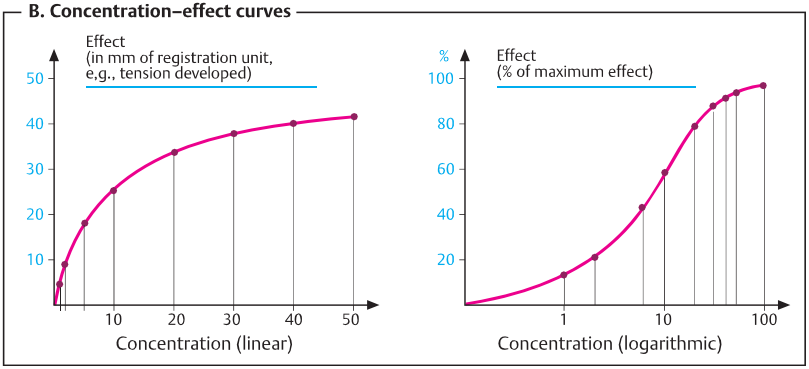

B. Concentration–effect curves
Effect
(in mm of registration unit,
e.g., tension developed)
50
40
30
20
10
10
20
30
40
50
Concentration (linear)
%
Effect
(% of maximum effect)
100
80
60
40
20
1
10
100
Concentration (logarithmic)

Fig. 8.2

Concentration–Binding Curves

In order to elicit their effect, drug molecules must be bound to the cells of the effector organ. Binding commonly occurs at specific cell structures, namely, the receptors. The analysis of drug binding to receptors aims to determine the affinity of ligands, the kinetics of interaction, and the characteristics of the binding site itself.

In studying the affinity and number of such binding sites, use is made of membrane suspensions of different tissues. This approach is based on the expectation that binding sites will retain their characteristic properties during cell homogenization.

Provided that binding sites are freely accessible in the medium in which membrane fragments are suspended, drug concentration at the "site of action" will equal that in the medium. The drug under study is radiolabeled (enabling low concentrations to be measured quantitatively), added to the membrane suspension, and allowed to bind to receptors. Membrane fragments and medium are then separated, e.g., by filtration, and the amount of bound drug (ligand) is measured. Binding increases in proportion to concentration as long as there is a negligible reduction in the number of free binding sites ($c \approx 1$ and $B \approx 10\%$ of maximum binding; $c \approx 2$ and $B \approx 20\%$). As binding sites approach saturation, the number of free sites decreases and the increment in binding is no longer proportional to the increase in concentration (in the example illustrated, an increase in concentration by 1 is needed to increase binding from 10% to 20%; however, an increase by 20 is needed to raise it from 70% to 80%).

The **law of mass action** describes the hyperbolic relationship between binding (B) and ligand concentration (c). This relationship is characterized by the drug's affinity ($1/K_D$) and the maximum binding (B_{max}), i.e., the total number of binding sites per unit of weight of membrane homogenate.

$$B = B_{max} \times \frac{c}{c + K_D} \qquad (8.1)$$

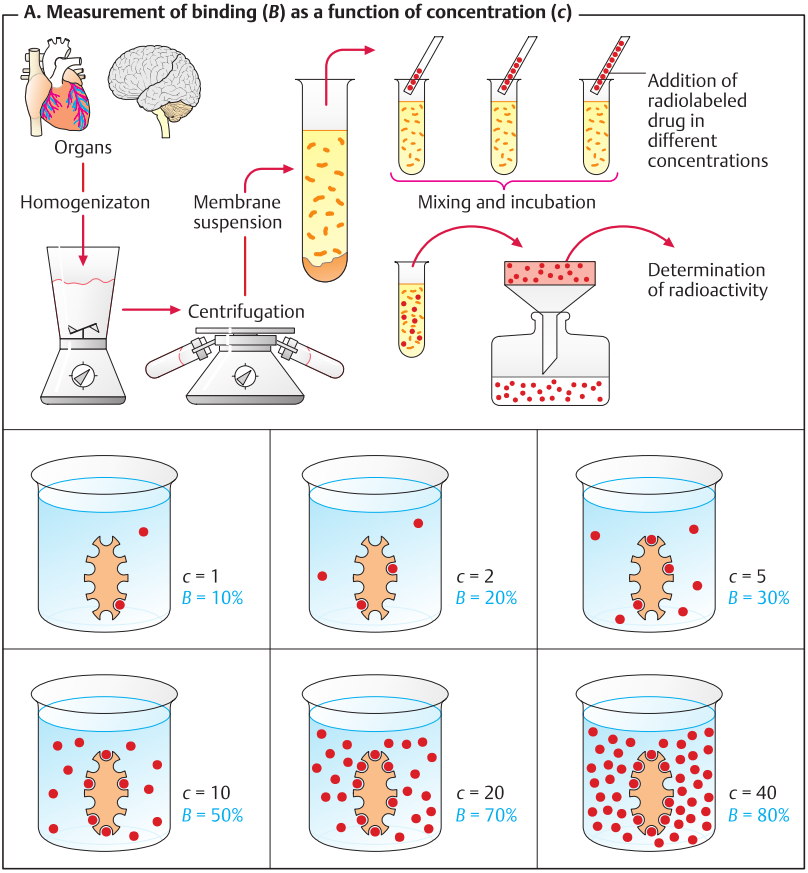
K_D is the equilibrium dissociation constant and corresponds to that ligand concentration at which 50% of binding sites are occupied. The values given in ▶ Fig. 8.3**A** and used for plotting the concentration–binding graph (▶ Fig. 8.3**B**) result when $K_D = 10$.

The differing affinity of different ligands for a binding site can be demonstrated elegantly by binding assays. Although simple to perform, these binding assays pose the difficulty of correlating unequivocally the binding sites concerned with the pharmacological effect; this is particularly difficult when more than one population of binding sites is present. Therefore, receptor binding must not be assumed until it can be shown that:

1. Binding is saturable (saturability).
2. The only substances bound are those possessing the same pharmacological mechanism of action (specificity).
3. Binding affinity of different substances is correlated with their pharmacological potency.

Binding assays provide information about the affinity of ligands, but they do not give any clue as to whether a ligand is an agonist or antagonist (p. 78).

Radiolabeled drugs bound to their receptors may be of help in purifying and analyzing further the receptor protein.


A. Measurement of binding (B) as a function of concentration (c)
Organs
Homogenizaton
Membrane suspension
Centrifugation
Addition of radiolabeled drug in different concentrations
Mixing and incubation
Determination of radioactivity
c = 1
B = 10%
c = 2
B = 20%
c = 5
B = 30%
c = 10
B = 50%
c = 20
B = 70%
c = 40
B = 80%

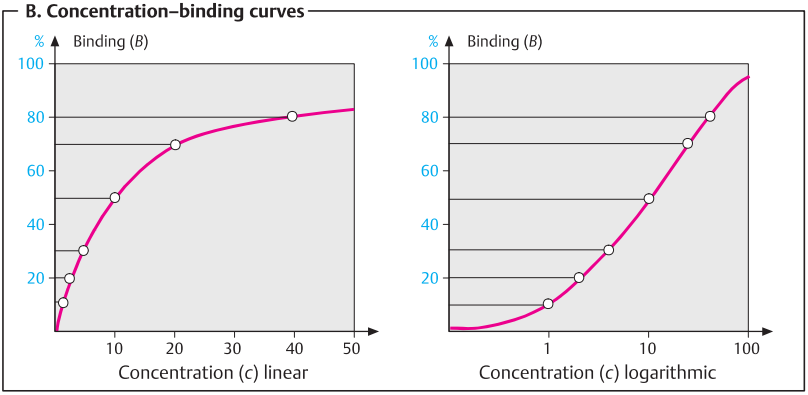

B. Concentration–binding curves
% Binding (B)
100
80
60
40
20
10
20
30
40
50
Concentration (c) linear
% Binding (B)
100
80
60
40
20
1
10
100
Concentration (c) logarithmic

Fig. 8.3

Types of Binding Forces

Unless a drug comes into contact with intrinsic structures of the body, it cannot affect body function.

Covalent Bonding

Two atoms enter a covalent bond if each donates an electron to a shared electron pair (cloud). This state is depicted in structural formulas by a dash. The covalent bond is "firm," that is, not reversible or poorly so. Few drugs are covalently bound to biological structures. The bond, and possibly the effect, persist for a long time after intake of a drug has been discontinued, making therapy difficult to control. Examples include alkylating cytostatic agents (p. 298) or organophosphates (p. 310). Conjugation reactions occurring in biotransformation (p. 56) also represent covalent linkages (e.g., to glucuronic acid).

Noncovalent Bonding

In noncovalent bonding there is no formation of a shared electron pair. The bond is reversible and is typical of most drug–receptor interactions. Since a drug usually attaches to its site of action by multiple contacts, several of the types of bonds described below may participate.

► **Electrostatic attraction** (► **Fig. 9.1A**). A positive and a negative charge attract each other.

Ionic interaction: An ion is a particle charged either positively (cation) or negatively (anion), i.e., the atom is deficient in electrons or has surplus electrons, respectively. Attraction between ions of opposite charge is inversely proportional to the square of the distance between them; it is the initial force drawing a charged drug to its binding site. Ionic bonds have a relatively high stability.

Dipole–ion interaction: When bonding electrons are asymmetrically distributed over the atomic nuclei involved, one atom will bear a negative (δ^-) and its partner a positive (δ^+) partial charge. The molecule thus presents a positive and a negative pole, i.e., it has polarity or is a dipole. A partial charge can interact electrostatically with an ion of opposite charge.

Dipole–dipole interaction is the electrostatic attraction between opposite partial charges. When a hydrogen atom bearing a partial positive charge bridges two atoms bearing partial negative charges, a hydrogen bond is created.

van der Waals bonds (► **Fig. 9.1B**) are formed between apolar molecular groups that have come into close proximity. Spontaneous transient distortion of electron clouds (momentary faint dipole, $\delta\delta$) may induce an opposite dipole in the neighboring molecule. The van der Waals bond, therefore, is also a form of electrostatic attraction, albeit of very low strength (inversely proportional to 7th power of distance).

► **Hydrophobic interaction** (► **Fig. 9.1C**). The attraction between the water dipoles is strong enough to hinder intercalation of any apolar (uncharged) molecules. By tending toward each other, H_2O molecules squeeze apolar particles from their midst. Accordingly, in the organism, apolar particles such as fatty acid chains of cell membranes or apolar regions of a receptor have an increased probability of remaining in nonaqueous, apolar surroundings.

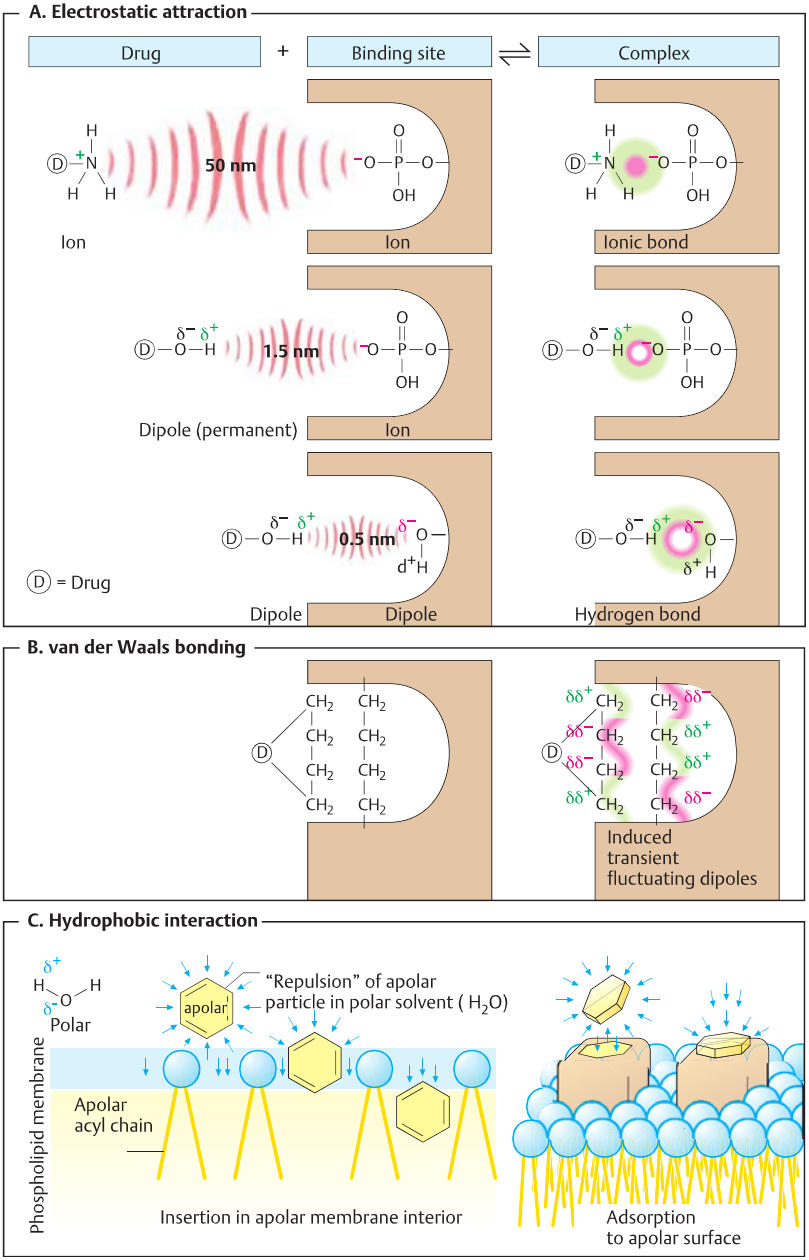

A. Electrostatic attraction
Drug
+
Binding site
Complex
50 nm
Ion
Ion
Ionic bond
1.5 nm
Dipole (permanent)
Ion
0.5 nm
Dipole
Dipole
Hydrogen bond
D = Drug
B. van der Waals bonding
Induced
transient
fluctuating dipoles
C. Hydrophobic interaction
Polar
apolar
"Repulsion" of apolar
particle in polar solvent (H2O)
Phospholipid membrane
Apolar
acyl chain
Insertion in apolar membrane interior
Adsorption
to apolar surface

Fig. 9.1

Agonists–Antagonists

An **agonist** (▶ Fig. 9.2**A**) has affinity (tendency to adhere) for a receptor and affects the receptor protein in such a manner as to change it to an active conformation—"**intrinsic activity**." The biological effect of the agonist (i.e., the change in cell function) depends on the effectiveness of signal transduction steps (p. 82) associated with receptor activation. The maximal effect of an agonist may already occur when only a fraction of the available receptors is occupied (▶ Fig. 9.2**B**, agonist A); this is described as the system's receptor reserve. Another agonist (agonist B), possessing equal affinity but less ability to activate the receptor and the associated signal transduction steps (i.e., less intrinsic activity, reduced coupling efficiency), will produce a smaller maximal effect even if all receptors are occupied—smaller **efficacy**. Agonist B is a *partial agonist*. The **potency** of an agonist is characterized by the concentration (EC_{50}) at which a half-maximal effect is attained.

Antagonists (▶ Fig. 9.2**B**) attenuate the effect of agonists: they act "antiagonistically." **Competitive antagonists** possess affinity for the receptors, but their binding does not elicit a change in cell function. In other words, they are devoid of intrinsic activity. When present simultaneously, an agonist and a competitive antagonist vie for occupancy of the receptor. The affinities and concentrations of both competitors determine whether binding of agonist or antagonist predominates. By increasing the concentration of the agonist, blockade induced by an antagonist can be surmounted (▶ Fig. 9.2**C**): that is, the concentration–effect curve of the agonist is shifted "right"—to higher concentrations—with preservation of the maximal effect.

Models of the Molecular Mechanism of Agonist/Antagonist Action

▶ **Agonist induces an active conformation.** The *agonist* binds to the inactive receptor and thereby causes the resting conformation to change into the active state. The *antagonist* attaches to the inactive receptor without altering its conformation.

▶ **Agonist stabilizes spontaneously occurring active conformation.** The receptor may spontaneously "flip" into the active conformation. Usually, however, the statistical probability of such an event is so small that a spontaneous excitation of the cells remains undetectable. Selective binding of the *agonist* can occur only to the active conformation and thus favors the existence of this state. The *antagonist* shows affinity only for the inactive state, promoting existence of the latter. If the system has little spontaneous activity, no measurable effect will result from adding an antagonist. However, if the system displays high spontaneous activity, the antagonist is liable to produce an effect opposite to that of an agonist: *inverse agonist*. A "true" antagonist without intrinsic activity ("neutral antagonist") displays equal affinity for the active and inactive conformations of the receptor and does not interfere with the basal activity of the cell. A **partial agonist** generates a receptor conformation between the "active" and "inactive" states, or it can occupy the receptor in two positions, an activating and a non-activating, with a certain statistical probability.

Other Forms of Antagonism

▶ **Allosteric antagonism.** The antagonist is bound outside the agonist's site of attachment at the receptor and induces a decrease in agonist affinity. The latter is increased in the case of **allosteric synergism**.

▶ **Functional antagonism.** Two agonists acting via different receptors affect the same variable (e.g., luminal diameter of bronchi) in opposite directions (epinephrine → dilation; histamine → constriction).

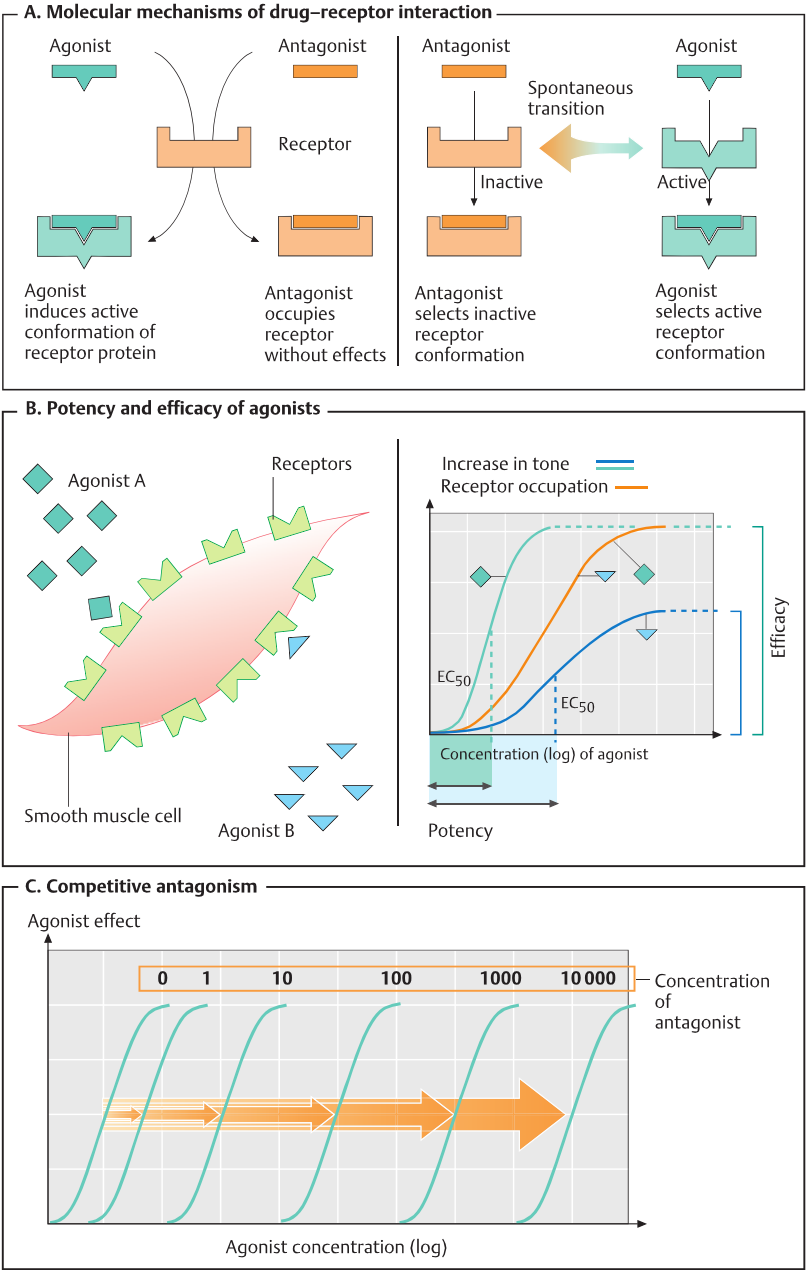

A. Molecular mechanisms of drug–receptor interaction
Agonist
Antagonist
Receptor
Agonist induces active conformation of receptor protein
Antagonist occupies receptor without effects
Antagonist
Spontaneous transition
Agonist
Inactive
Active
Antagonist selects inactive receptor conformation
Agonist selects active receptor conformation
B. Potency and efficacy of agonists
Agonist A
Receptors
Smooth muscle cell
Agonist B
Increase in tone
Receptor occupation
EC50
EC50
Efficacy
Concentration (log) of agonist
Potency
C. Competitive antagonism
Agonist effect
0
1
10
100
1000
10 000
Concentration of antagonist
Agonist concentration (log)

Fig. 9.2

Enantioselectivity of Drug Action

Many drugs are racemates, including β-blockers, nonsteroidal anti-inflammatory agents, as well as the α_2-adrenoceptor agonist *medetomidine* (▶ Fig. 9.3**A**). A **racemate** consists of a molecule and its corresponding mirror image which, like the left and right hands, cannot be superimposed. Such **chiral** ("handed") pairs of molecules are referred to as **enantiomers**. Typically, chirality is due to a single carbon (C) atom bonded to four different substituents *(asymmetric carbon atom)*. Enantiomerism is a special case of stereoisomerism. Nonchiral stereoisomers are called **diastereomers** (e.g., quinidine/quinine).

Bond lengths in enantiomers, but not necessarily diastereomers, are the same. Therefore, enantiomers possess **similar physicochemical properties** (e.g., solubility, melting point) and both forms are usually obtained in equal amounts by chemical synthesis. As a result of enzymatic activity, however, only one of the enantiomers is usually found in nature.

In solution, enantiomers **rotate the plane of oscillation of linearly polarized light in opposite directions**; hence they are referred to as *"dextro-rotatory"* or *"levo-rotatory,"* designated by the prefixes *d*- or (+)- and *l*-or (**–**)-, respectively. The direction of rotation gives no clue concerning the spatial structure of enantiomers. The *absolute* configuration, as determined by certain rules, is described by the prefixes (*S*)- and (*R*)-. In some compounds, designation as the D-and L-forms is possible by reference to the structure of D-and L-glyceraldehyde.

For drugs to exert biological actions, contact with reaction partners in the body is required. When the reaction favors one of the enantiomers, *enantioselectivity* is observed.

▶ **Enantioselectivity of affinity.** If a receptor has sites for three of the substituents (symbolized in ▶ Fig. 9.3**B** by a cone, sphere, and cube) on the asymmetric carbon to attach to, only one of the enantiomers will have optimal fit. Its affinity will then be higher. Thus, *dexmedetomidine* displays an affinity at the α_2-adrenoceptors (p. 114) almost 40 times that of levomedetomidine. The dexmedetomidine enantiomer is used in humans as a hypnotic (p. 344), whereas the racemate *medetomidine* is used in veterinary medicine. Propranolol is another example of a drug enantiomer with different receptor affinity: (*S*)-(**–**)-propranolol has an affinity 100 times that of the (*R*)-(+) form.

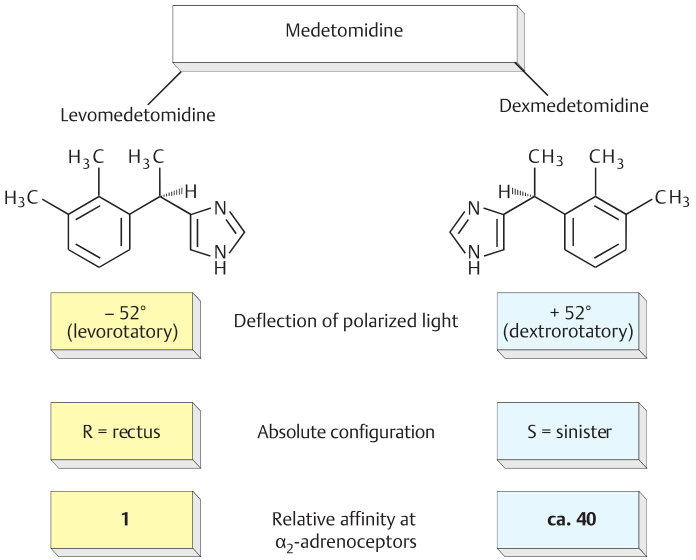
▶ **Enantioselectivity of intrinsic activity.** The mode of attachment at the receptor also determines whether an effect is elicited; and whether or not a substance has intrinsic activity, i.e., acts as an agonist or antagonist. For instance, (–)-*dobutamine* is an agonist at β-adrenoceptors, whereas the (+)-enantiomer is an antagonist.

▶ **Inverse enantioselectivity at another receptor.** An enantiomer may possess an unfavorable configuration at one receptor that may, however, be optimal for interaction with another receptor. In the case of *dobutamine,* the (+)-enantiomer has affinity at β-adrenoceptors that is 10 times higher than that of the (**–**)-enantiomer, both having agonist activity. However, the α-adrenoceptor stimulant action is due to the (**–**)-form (see above).

As described for receptor interactions, enantioselectivity may also be manifested in drug interactions with **enzymes** and **transport proteins**. Enantiomers may display different affinities and reaction velocities.

▶ **Conclusion.** The enantiomers of a racemate can differ sufficiently in their pharmacodynamic and pharmacokinetic properties to constitute two distinct drugs.

A. Example of an enantiomeric pair with different affinities for a stereoselective receptor



B. Reasons for different pharmacological properties of enantiomers

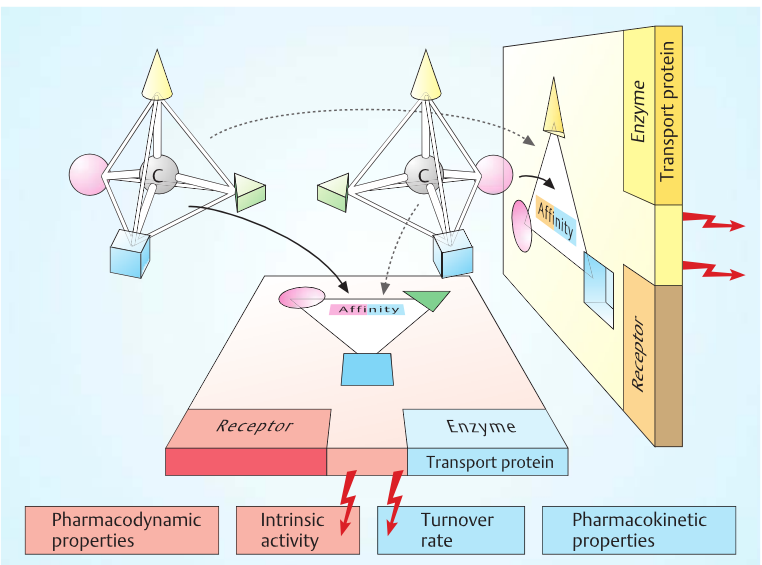


Fig. 9.3

Receptor Types

Receptors are macromolecules that operate to bind mediator substances and transduce this binding into an effect, i.e., a change in cell function. Receptors differ in terms of their structure and the manner in which they translate occupancy by a ligand into a cellular response (**signal transduction**).

G-Protein-coupled receptors (▶ Fig. 9.4**A**) consist of an amino acid chain that weaves in and out of the membrane in serpentine fashion. The extramembranal loop regions of the molecule may possess sugar residues at different N-glycosylation sites. The seven α-helical membrane-spanning domains form a circle around a central pocket that carries the attachment sites for the mediator substance. Binding of the mediator molecule or of a structurally related agonist molecule induces a change in the conformation of the receptor protein, enabling the latter to interact with a G-protein (= guanyl nucleotide-binding protein). G-proteins lie at the inner leaf of the plasmalemma and consist of three subunits designated α, β, and γ. There are various G-proteins that differ mainly with regard to their α-unit. Association with the receptor activates the G-protein, leading in turn to activation of another protein (enzyme, ion channel). A large number of mediator substances act via G-protein-coupled receptors.

An example of a **ligand-gated ion channel** (▶ Fig. 9.4**B**) is the nicotinic cholinoceptor of the motor end plate. The receptor complex consists of five subunits, each of which contains four transmembrane domains. Simultaneous binding of two acetylcholine (ACh) molecules to the two α-subunits results in opening of the ion channel with entry of Na^+ (and exit of some K^+), membrane depolarization, and triggering of an action potential (p. 192). The neuronal *N*-cholinoceptors apparently consist only of α- and β-subunits. Some of the receptors for the transmitter γ-aminobutyric acid (GABA) belong to this receptor family: the $GABA_A$ subtype is a chloride channel (and also contains a benzodiazepine binding site, see p. 222). Glutamate and glycine both act via ligand-gated ion channels.

The insulin receptor protein represents a **ligand-regulated enzyme** (▶ Fig. 9.4**C**), a catalytic receptor. When insulin binds to the extracellular attachment site, a tyrosine kinase activity is "switched on" at the intracellular portion. Protein phosphorylation leads to altered cell function via the assembly of other signal proteins. Receptors for growth hormones also belong to the catalytic receptor class.

Protein synthesis-regulating receptors (▶ Fig. 9.4**D**) for steroids and thyroid hormone are found in the cytosol and in the cell nucleus, respectively. The receptor proteins are located intracellularly; depending on the hormone, either in the cytosol (e.g., glucocorticoids, mineralocorticoids, androgens, and gestagens) or in the cell nucleus (e.g., estrogens, thyroid hormone). Binding of hormone exposes a normally hidden domain of the receptor protein, thereby permitting the latter to bind to a particular DNA nucleotide sequence on a gene and to regulate its transcription. The ligand-receptor complexes thus function as transcription regulating factors. Transcription is usually initiated or enhanced, rarely blocked.

The hormone-receptor complexes interact pairwise with DNA. These pairs (dimers) may consist of two identical hormone-receptor complexes (homodimeric form, e.g., with adrenal or gonadal hormones). The thyroid hormone-receptor complex occurs in heterodimeric form and combines with a *cis*-retinoic acid-receptor complex.

▶ **Topography of ligand binding.** The receptor site through which an endogenous messenger elicits activation of the receptor protein is called orthosteric. Most pharmacological receptor agonists and antagonists use the orthosteric area. Ligands that act by docking to a different receptor region are classified as allosteric. If the two binding sites are adjacent, they can be occupied at the same time by suitable ligands; this is known as dualsteric or bitopical binding.

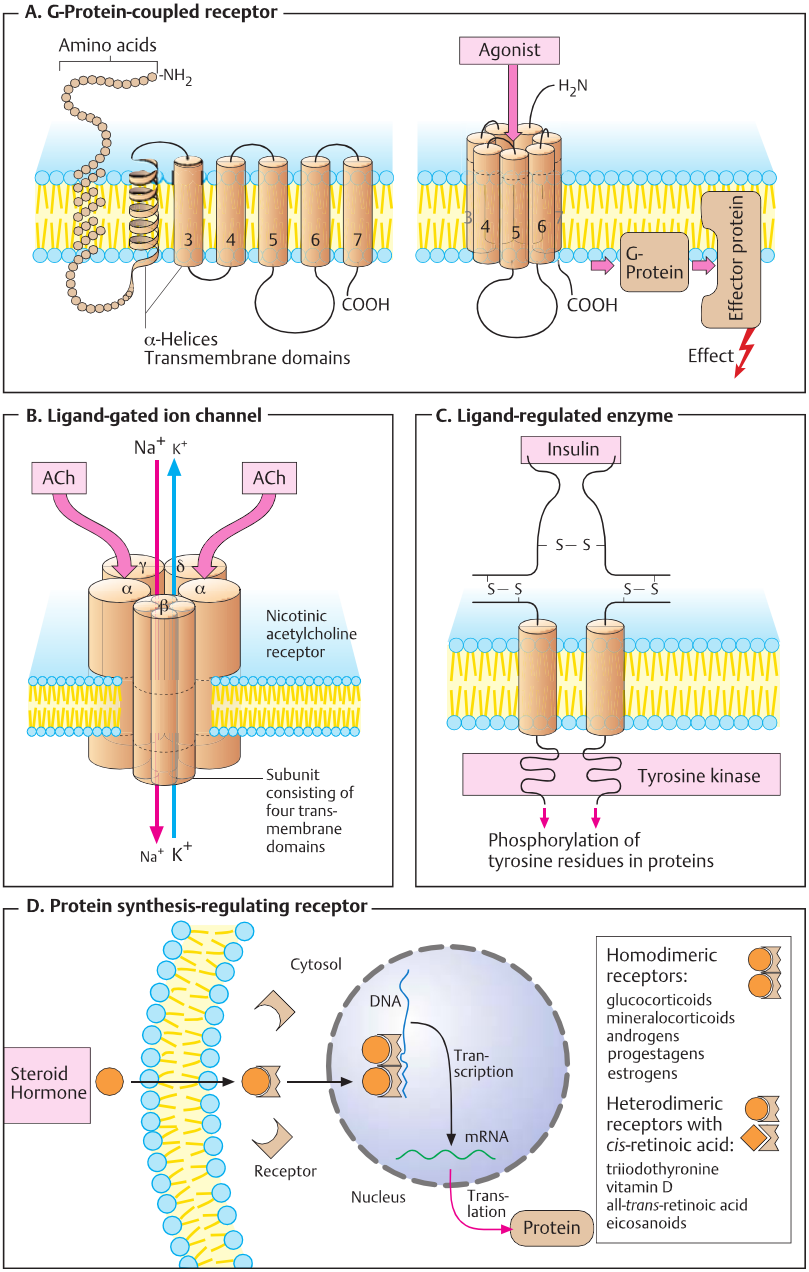

A. G-Protein-coupled receptor
Amino acids
NH2
3
4
5
6
7
COOH
α-Helices
Transmembrane domains
Agonist
H2N
3
4
5
6
G-Protein
Effector protein
COOH
Effect
B. Ligand-gated ion channel
Na+ K+
ACh
ACh
γ
δ
α
α
β
Nicotinic acetylcholine receptor
Subunit consisting of four trans-membrane domains
Na+ K+
C. Ligand-regulated enzyme
Insulin
S – S
S – S
S – S
Tyrosine kinase
Phosphorylation of tyrosine residues in proteins
D. Protein synthesis-regulating receptor
Steroid Hormone
Cytosol
Receptor
DNA
Tran-scription
mRNA
Nucleus
Trans-lation
Protein
Homodimeric receptors:
glucocorticoids
mineralocorticoids
androgens
progestagens
estrogens
Heterodimeric receptors with cis-retinoic acid:
triiodothyronine
vitamin D
all-trans-retinoic acid
eicosanoids

Fig. 9.4

Mode of Operation of G-Protein-coupled Receptors

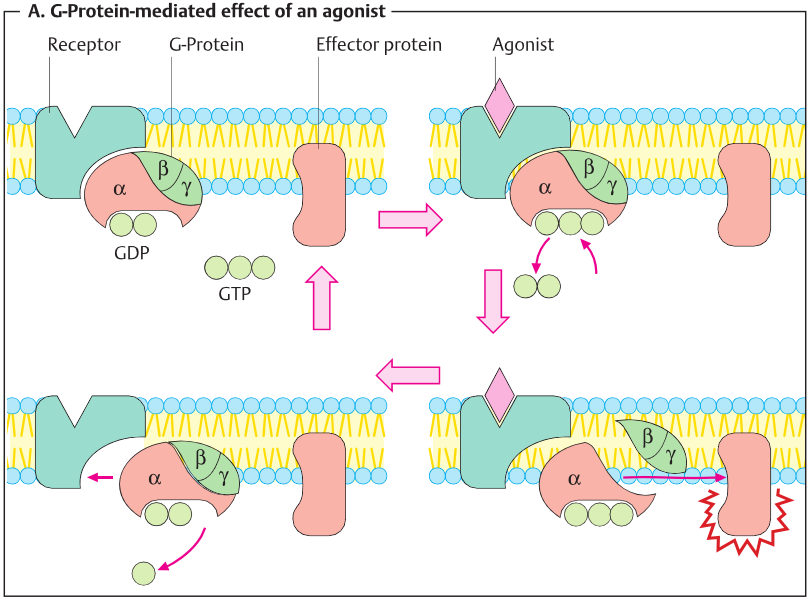
Signal transduction at G-protein-coupled receptors uses essentially the same basic mechanism (▶ Fig. 9.5**A**). Agonist binding to the receptor leads to a change in receptor protein conformation. This change propagates to the G-protein: the α-subunit exchanges GDP for GTP, then dissociates from the two other subunits, associates with an effector protein and alters its functional state. In principle, the β- and γ-subunits are also able to interact with effector proteins. The α-subunit slowly hydrolyses bound GTP to GDP. G_{α}-GDP has no affinity for the effector protein and re-associates with the β- and γ-subunits (▶ Fig. 9.5**A**). G-proteins can undergo lateral diffusion in the membrane; they are not assigned to individual receptor proteins. However, a relation exists between receptor types and G-protein types (▶ Fig. 9.5**B**). Furthermore, the α-subunits of individual G-proteins are distinct in terms of their affinity for different effector proteins, as well as the kind of influence exerted on the effector protein. G_{α}-GTP of the G_s-protein stimulates adenylyl cyclase, while G_{α}-GTP of the G_i-protein is inhibitory. The G-protein-coupled receptor family includes muscarinic cholinoceptors, adrenoceptors for norepinephrine and epinephrine, as well as receptors for dopamine, histamine, serotonin, glutamate, GABA, morphine, prostaglandins, leukotrienes, and many other mediators and hormones.

Major effector proteins for G-protein-coupled receptors include **adenylyl cyclase** (ATP → intracellular messenger **cAMP**), **phospholipase C** (phosphatidylinositol → intracellular messengers **inositol trisphosphate** and **diacylglycerol**), as well as ion channel proteins (▶ Fig. 9.5**B**). Numerous cell functions are regulated by cellular cAMP concentration, because cAMP enhances activity of protein kinase A, which catalyzes the transfer of phosphate groups onto functional proteins. Elevation of cAMP levels leads to relaxation of smooth muscle tonus, enhanced contractility of cardiac muscle, as well as increased glycogenosis and lipolysis (p. 108). Phosphorylation of cardiac calcium channel proteins increases the probability of channel opening during membrane depolarization. It should be noted that cAMP is inactivated by phosphodiesterase. Inhibitors of this enzyme elevate intracellular cAMP concentration and elicit effects resembling those of epinephrine.

The receptor protein itself may undergo phosphorylation, with a resultant loss of its ability to activate the associated G-protein. This is one of the mechanisms that contribute to a decrease in sensitivity of a cell during prolonged receptor stimulation by an agonist *(desensitization)*.

G_q-mediated activation of phospholipase C leads to cleavage of the membrane phospholipid phosphatidylinositol 4,5-bisphosphate into **inositol trisphosphate** (IP_3) and **diacylglycerol** (DAG). IP_3 promotes release of Ca^{2+} from storage organelles, whereby contraction of smooth muscle cells, breakdown of glycogen, or exocytosis may be initiated. DAG stimulates protein kinase C, which phosphorylates certain serine- or threonine-containing enzymes.

Certain G-proteins can induce opening of **channel proteins**. In this way, potassium channels can be activated, e.g., acetylcholine effect on sinus node (p. 120); opioid effect on neural impulse transmission (p. 210).


A. G-Protein-mediated effect of an agonist
Receptor
G-Protein
Effector protein
Agonist
α
β
γ
GDP
GTP

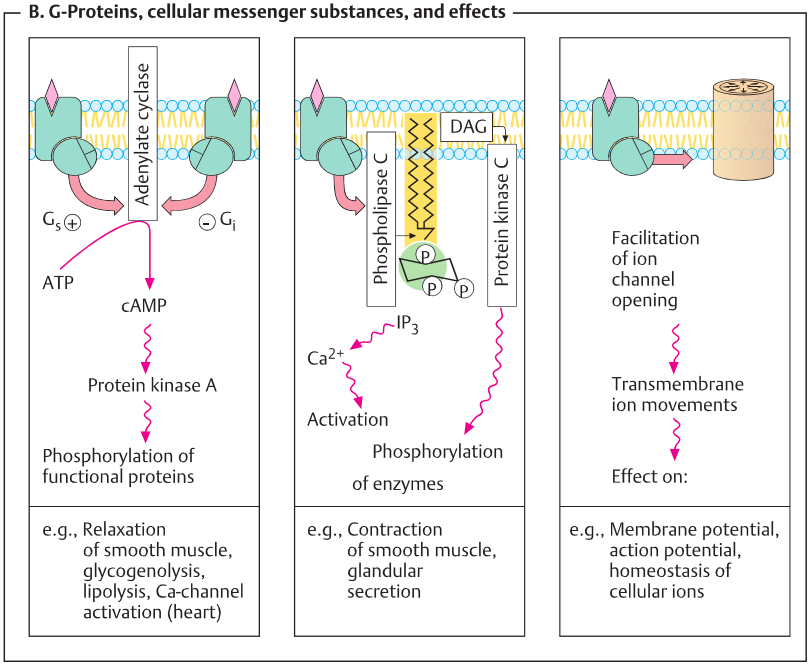

B. G-Proteins, cellular messenger substances, and effects
Adenylate cyclase
G_s ⊕
⊖ G_i
ATP
cAMP
Protein kinase A
Phosphorylation of functional proteins
e.g., Relaxation of smooth muscle, glycogenolysis, lipolysis, Ca-channel activation (heart)
Phospholipase C
DAG
Protein kinase C
P
IP3
Ca^{2+}
Activation
Phosphorylation of enzymes
e.g., Contraction of smooth muscle, glandular secretion
Facilitation of ion channel opening
Transmembrane ion movements
Effect on:
e.g., Membrane potential, action potential, homeostasis of cellular ions

Fig. 9.5

Time Course of Plasma Concentration and Effect

After the administration of a drug, its concentration in plasma rises, reaches a peak, and then declines gradually to the starting level, owing to the processes of distribution and elimination (p. 64). Plasma concentration at a given point in time depends on the dose administered. Many drugs exhibit a linear relationship between plasma concentration and dose within the therapeutic range (**dose-linear kinetics** [▶ Fig. 9.6**A**]; note different scales on ordinate). However, the same does not apply to drugs whose elimination processes are already sufficiently activated at therapeutic plasma levels so as to preclude further proportional increases in the rate of elimination when the concentration is increased further. Under these conditions, a smaller proportion of the dose administered is eliminated per unit time.

A model example of this behavior is the elimination of ethanol (p. 62). Because the metabolizing enzyme, alcohol dehydrogenase, is already saturated at low ethanol concentrations, only the same amount per unit time is broken down despite rising concentrations.

The time courses of the *effect* and of the *concentration* in plasma are not identical, because the concentration–effect relationship is complex (e.g., with a threshold phenomenon) and often obeys a hyperbolic function (▶ Fig. 9.6**B**). This means that the time course of the effect exhibits dose dependence also in the presence of dose-linear kinetics (▶ Fig. 9.6**C**).

In the lower dose range (example 1), the plasma level passes through a concentration range (0–0.9) in which the change in concentration still correlates quasi-linearly with the change in effect. The time courses of the concentration in plasma and the effect (▶ Fig. 9.6**A** and ▶ Fig. 9.6**C**, left graphs) are very similar. However, after a high dose (100), the plasma level will remain in a concentration range (between 90 and 20) where changes in concentration do not evoke significant changes in effect.

Accordingly, the time-effect curve displays a kind of plateau after high doses (100). The effect only begins to wane after the plasma level has fallen to a range (below 20) in which changes in plasma level are reflected in the intensity of the effect.

The dose dependence of the time course of the drug effect is exploited when the duration of the effect is to be prolonged by administration of a dose in excess of that required for the effect. This is done in the case of penicillin G (p. 268), when a dosing interval of 8 hours is recommended although the drug is eliminated with a half-life of 30 minutes. This procedure is, of course, feasible only if supramaximal dosing is not associated with toxic effects.

It follows that a nearly constant effect can be achieved, although the plasma level may fluctuate greatly during the interval between doses.

The hyperbolic relationship between plasma concentration and effect explains why the time course of the effect, unlike that of the plasma concentration, cannot be described in terms of a simple exponential function. A half-life can only be given for the processes of drug absorption and elimination, hence the change in plasma levels, but generally not for the onset or decline of the effect.

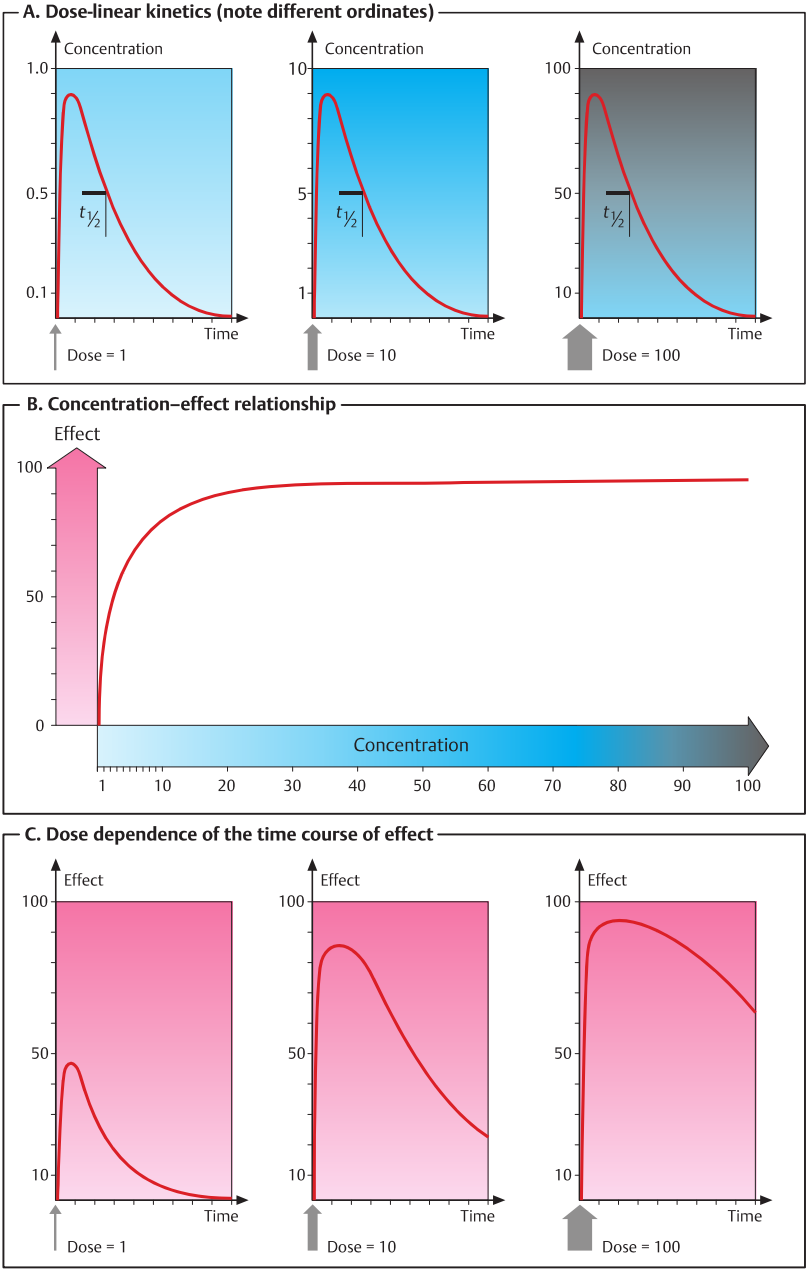

A. Dose-linear kinetics (note different ordinates)
Concentration
1.0
0.5
0.1
$t_{1/2}$
Time
Dose = 1
Concentration
10
5
1
$t_{1/2}$
Time
Dose = 10
Concentration
100
50
10
$t_{1/2}$
Time
Dose = 100
B. Concentration–effect relationship
Effect
100
50
0
Concentration
1
10
20
30
40
50
60
70
80
90
100
C. Dose dependence of the time course of effect
Effect
100
50
10
Time
Dose = 1
Effect
100
50
10
Time
Dose = 10
Effect
100
50
10
Time
Dose = 100

Fig. 9.6

Adverse Drug Effects, Side Effects

The desired (or intended) principal effect of any drug is to modify body function in such a manner as to alleviate symptoms caused by the patient's illness. In addition, a drug may also elicit unwanted effects that in turn may cause complaints, provoke illness, or even lead to death.

► **Causes of Adverse Effects: Overdosage** (► **Fig. 10.1A**). The drug is administered in a higher dose than is required for the principal effect; this directly or indirectly affects other body functions.

For instance, **morphine** (p. 210), given in the appropriate dose, affords excellent pain relief by influencing nociceptive pathways in the CNS. In excessive doses, it inhibits the respiratory center and makes apnea imminent. The dose dependence of both effects can be graphed in the form of dose–response curves (DRCs). The distance between the two DRCs indicates the difference between the therapeutic and toxic doses. This *margin of safety* ("therapeutic index") indicates the risk of toxicity when standard doses are exceeded.

It should be noted that, apart from the amount administered, the rate of drug delivery is important. The faster blood levels rise, the higher concentrations will climb (see ► Fig. 7.2**B**). Rather than being required therapeutically, the initial concentration peak following i.v. injection of morphine-like agents causes side effects, e.g., intoxication (p. 210) and respiratory depression.

"The dose alone makes the poison" (Paracelsus). This holds true for both medicines and environmental poisons. *No substance as such is toxic!* In order to assess the risk of toxicity, knowledge is required of: (1) the effective dose during exposure; (2) the dose level at which damage is likely to occur.

► **Increased sensitivity** (► **Fig. 10.1B**). If certain body functions develop hyperreactivity, unwanted effects can occur even at normal dose levels. Increased sensitivity of the respiratory center to morphine is found in patients with chronic lung disease, in neonates, or during concurrent exposure to other respiratory depressant agents. The DRC is shifted to the left and a smaller dose of morphine is sufficient to paralyze respiration. Genetic anomalies of metabolism may also lead to hypersensitivity; cf. pharmacogenetics (p. 96). The above forms of hypersensitivity must be distinguished from allergies involving the immune system (p. 90).

► **Lack of selectivity** (► **Fig. 10.1C**). Despite appropriate dosing and normal sensitivity, undesired effects can occur because the drug does not specifically act on the targeted (diseased) tissue or organ. For instance, the anticholinergic atropine is bound only to acetylcholine receptors of the muscarinic type; however, these are present in many different organs. Moreover, the neuroleptic chlorpromazine is able to interact with several different receptor types. Thus, its action is neither organ-specific nor receptor-specific.

The consequences of lack of selectivity can often be avoided if the drug does not require the blood route to reach the target organ but is, instead, applied locally, as in the administration of parasympatholytics in the form of eye drops or in an aerosol for inhalation.

Side effects that arise as a consequence of a known mechanism of action are plausible and the connection with drug ingestion is simple to recognize. It is more difficult to detect unwanted effects that arise from an unknown action. Some compelling examples of these include fetal damage after taking a hypnotic (thalidomide), pulmonary hypertension after appetite depressants, and fibrosis after antimigraine drugs.

With every drug use, unwanted effects must be taken into account. Before prescribing a drug, the physician should therefore do a **risk–benefit analysis**.

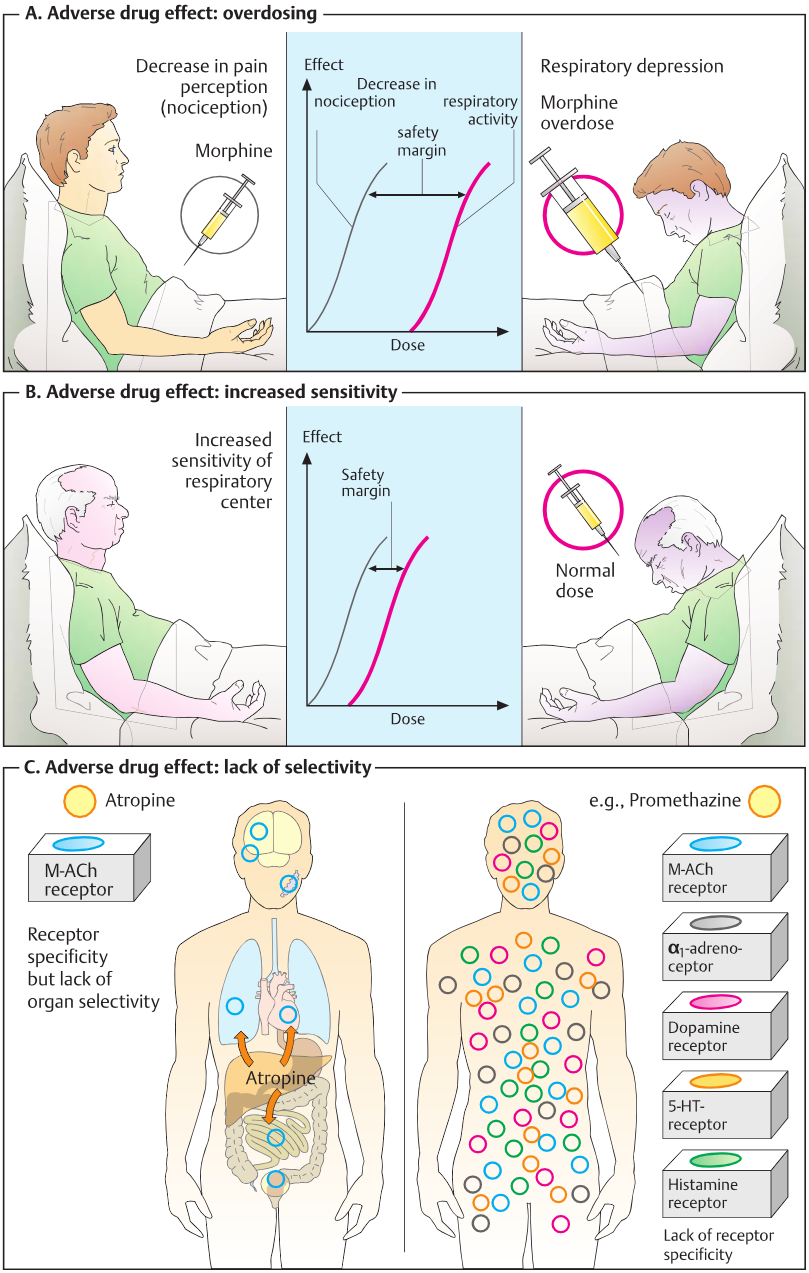

A. Adverse drug effect: overdosing
Decrease in pain perception (nociception)
Morphine
Effect
Decrease in nociception
respiratory activity
safety margin
Dose
Respiratory depression
Morphine overdose
B. Adverse drug effect: increased sensitivity
Increased sensitivity of respiratory center
Effect
Safety margin
Dose
Normal dose
C. Adverse drug effect: lack of selectivity
Atropine
M-ACh receptor
Receptor specificity but lack of organ selectivity
Atropine
e.g., Promethazine
M-ACh receptor
α1-adreno-ceptor
Dopamine receptor
5-HT-receptor
Histamine receptor
Lack of receptor specificity

Fig. 10.1

Drug Allergy

The immune system normally functions to inactivate and remove high-molecular-weight "foreign" matter taken up by the organism. Immune responses can, however, occur without appropriate cause or with exaggerated intensity and may harm the organism; for instance, when allergic reactions are caused by drugs (active ingredient or pharmaceutical excipients). Only a few drugs, e.g., (heterologous) proteins, have a molecular weight large enough to act as effective **antigens** or **immunogens**, capable by themselves of initiating an immune response. Most drugs or their metabolites (so-called **haptens**) must first be converted to an antigen by linkage to a body protein. In the case of penicillin G, a cleavage product (penicilloyl residue) probably undergoes covalent binding to protein.

During **initial contact** with the drug, the immune system is sensitized: antigen-specific lymphocytes of the T-type and B-type (antibody formation) proliferate in lymphatic tissue and some of them remain as so-called memory cells. Usually, these processes remain clinically silent.

During the **second contact**, antibodies are already present and memory cells proliferate rapidly. A detectable immune response—the allergic reaction—occurs. This can be of severe intensity, even at a low dose of the antigen. Four types of reactions can be distinguished:

► **Type 1, anaphylactic reaction.** Drug-specific antibodies of the *IgE-type* combine via their Fc moiety with receptors on the surface of *mast cells.* Binding of the drug provides the stimulus for the release of histamine (p. 130) and other mediators. In the most severe form, a life-threatening anaphylactic shock develops, accompanied by hypotension, bronchospasm (asthma attack), laryngeal edema, urticaria, stimulation of gut musculature, and spontaneous bowel movements.

► **Type 2, cytotoxic reaction.** *Drug-antibody (IgG) complexes* adhere to the surface of *blood cells,* where either circulating drug molecules or complexes already formed in blood accumulate. These complexes mediate the *activation of complement,* a family of proteins that circulate in the blood in an inactive form, but can be activated in a cascadelike succession by an appropriate stimulus. Activated complement, normally directed against microorganisms, can *destroy the cell membranes* and thereby cause cell death; it also promotes phagocytosis, attracts neutrophil granulocytes (chemotaxis), and stimulates other inflammatory responses. Activation of complement on blood cells results in their destruction, evidenced by hemolytic anemia, agranulocytosis, and thrombocytopenia.

► **Type 3, immune-complex vasculitis (serum sickness, Arthus reaction).** *Drug-antibody complexes* precipitate on *vascular walls, complement* is activated, and an *inflammatory reaction* is triggered. Attracted neutrophils, in a futile attempt to phagocytose the complexes, liberate lysosomal enzymes that damage the vascular walls (inflammation, vasculitis). Symptoms may include fever, exanthema, swelling of lymph nodes, arthritis, nephritis, and neuropathy.

► **Type 4, contact dermatitis.** A cutaneously applied drug is bound to the surface of *T-lymphocytes* directed specifically against it. The lymphocytes release signal molecules *(lymphokines)* into their vicinity that activate macrophages and provoke an inflammatory reaction.

Remarkably, virtually no drug group is completely free of allergic side effects. However, some chemical structures are prone to cause allergic reactions.

A. Adverse drug effect: allergic reaction

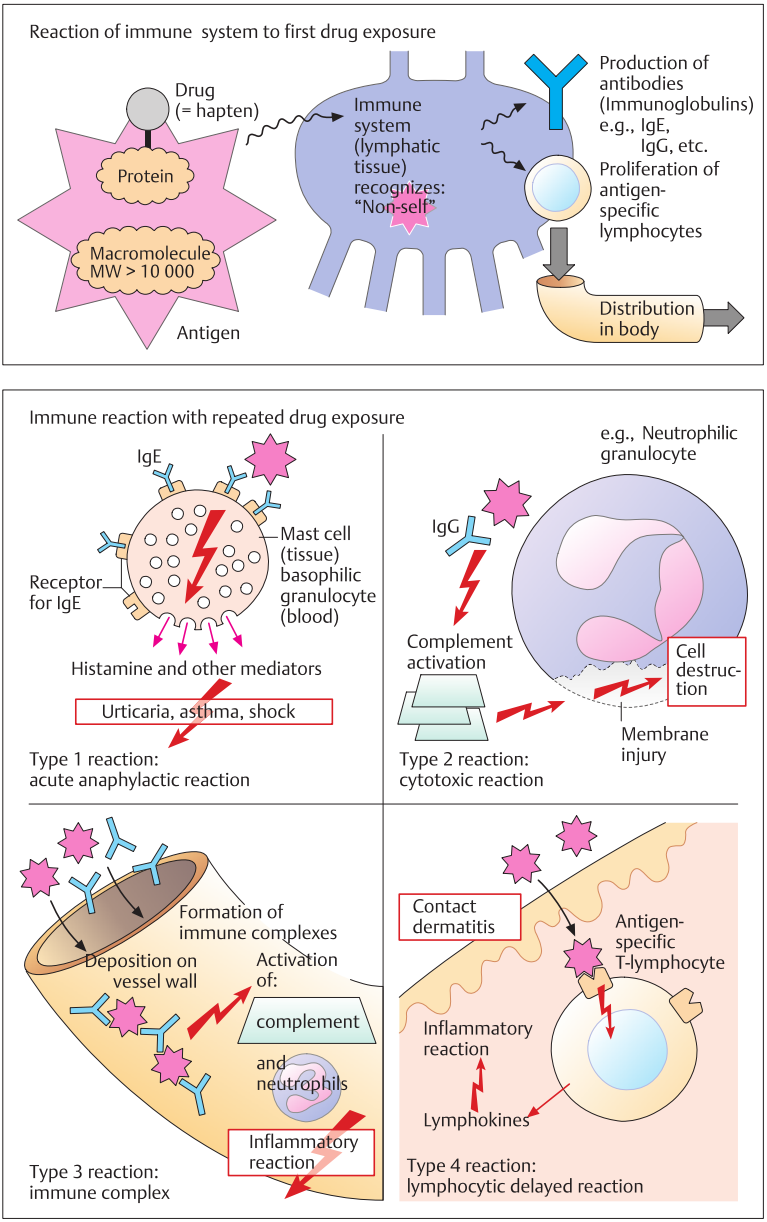


Fig. 10.2

Cutaneous Reactions

Upon systemic distribution, many drugs evoke skin reactions that are caused on an immunological basis. Moreover, cutaneous injury can also arise from nonimmunological mechanisms. Cutaneous side effects vary in severity from harmless to lethal. Cutaneous reactions are a common form of drug adverse reaction. Nearly half of them are attributed to antibiotics or sulfonamides, and one-third to nonsteroidal anti-inflammatory agents, with many other pharmaceuticals joining the list.

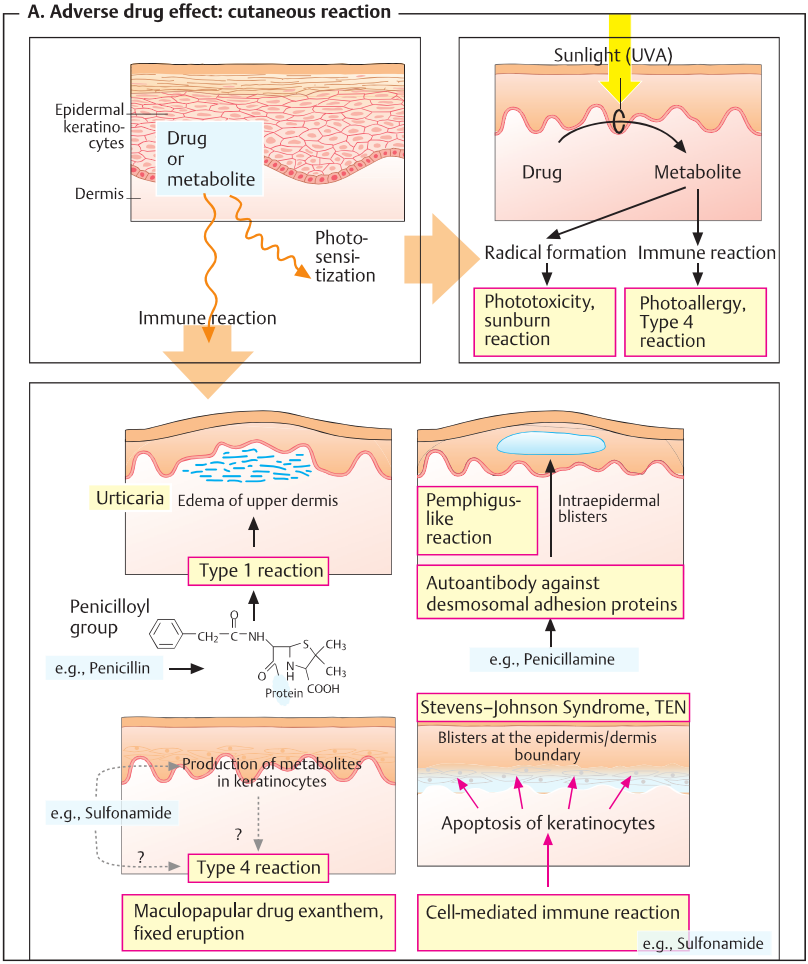
The following clinical conditions are noted:

- **Toxic erythema** with a maculopapular rash similar to that of measles and scarlet fever (▶ Fig. 10.3**B**, left; the most common clinical condition).
- **Urticaria** with itchy wheals as part of a Type 1 reaction including anaphylactic shock.
- **Fixed eruptions** (drug exanthems) with mostly a few demarcated, painful lesions, that may also be located in intertriginous skin regions (genital area, mucous membranes). With repeated exposure, these typically recur at the same sites.
- **Steven–Johnson syndrome** (SJS, erythema multiforme) and **toxic epidermal necrolysis** (TEN or **Lyell syndrome**) with apoptosis of keratinocytes and bullous detachment of the epidermis from the dermis. When more than 30% of the body surface is affected, TEN is present. Its course is dramatic and the outcome not rarely fatal.

The aforementioned reactions are thought to involve the following pathogenetic mechanisms. With penicillins, opening of the β-lactam bond is possible. The resulting penicilloyl group binds as a hapten to a protein. This may lead to an Ig-E-mediated **anaphylactic reaction**, manifested on the skin as urticaria.

Biotransformation via cytochrome oxidase may yield reactive products. Presumably keratinocytes are capable of such metabolic reactions. In this way, the para-amino group of sulfonamides can be converted into a hydroxyl amine group, which then acts as a hapten to induce a Type 4 reaction in the skin. Fixed maculopapular lesions are thought to arise on this basis.

- **Pemphigus-like** manifestations with formation of blisters. The development of cutaneous manifestations is not as ominous as in SJS or TEN, the blisters being located intraepidermally. This condition involves the formation of autoantibodies directed against adhesion proteins (desmoglein) of desmosomes, which link keratinocytes to each other. D-penicillamine and rifampicin are inducers of the rare drug-associated pemphigus (p. 308).
- **Photosensitivity** reactions result from exposure to sunlight, in particular the UVA component. In **phototoxic** reactions, drug molecules absorb photic energy and turn into reactive compounds that damage skin cells at their site of production. Plant constituents can also trigger phototoxic reactions. A large number of species from various plant families contain substances that can cause cell damage in the skin under the influence of sunlight. These include *Heracleum* species (e.g., *Heracleum sphondylium,* common hogweed) and St. John's wort *(Hypericum perforatum).* The latter is a well-known herbal medicine. In **photoallergic** reactions, photoreaction products bind covalently to proteins as haptens and trigger Type 4 allergic responses. The type and localization are difficult to predict.


A. Adverse drug effect: cutaneous reaction
Epidermal keratino-cytes
Drug or metabolite
Dermis
Photo-sensi-tization
Immune reaction
Sunlight (UVA)
Drug
Metabolite
Radical formation
Immune reaction
Phototoxicity, sunburn reaction
Photoallergy, Type 4 reaction
Urticaria
Edema of upper dermis
Type 1 reaction
Penicilloyl group
e.g., Penicillin
Protein
Pemphigus-like reaction
Intraepidermal blisters
Autoantibody against desmosomal adhesion proteins
e.g., Penicillamine
Stevens–Johnson Syndrome, TEN
Blisters at the epidermis/dermis boundary
Apoptosis of keratinocytes
Production of metabolites in keratinocytes
e.g., Sulfonamide
Type 4 reaction
Maculopapular drug exanthem, fixed eruption
Cell-mediated immune reaction
e.g., Sulfonamide

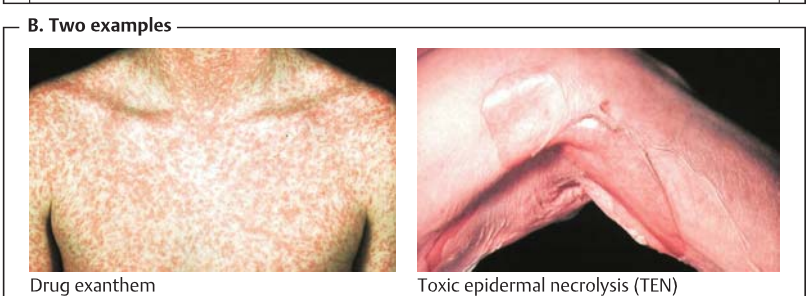

B. Two examples
Drug exanthem
Toxic epidermal necrolysis (TEN)

Fig. 10.3

Drug Toxicity in Pregnancy and Lactation: Effects on the fetus or the neonate

Drugs taken by the mother can be passed on transplacentally or via breast milk and can adversely affect the unborn or the neonate.

► **Pregnancy** (► **Fig. 10.4A**). Limb malformations induced by the hypnotic thalidomide (Contergan) first focused attention on the potential of drugs to cause malformations *(teratogenicity)*. Drug effects on the unborn fall into two basic categories:

1. Predictable effects that derive from the known pharmacological drug properties. Examples include masculinization of the female fetus by androgenic hormones; brain hemorrhage due to oral anticoagulants; bradycardia due to β-blockers.
2. Effects that specifically affect the developing organism and that cannot be predicted on the basis of the known pharmacological activity profile.

In assessing the risks attending drug use during pregnancy, the following points have to be considered:

a) *Time of drug use.* The possible sequelae of exposure to a drug depend on the stage of fetal development, as shown in ► Fig. 10.4**A**. Thus, the hazard posed by a drug with a specific action is limited in time, as illustrated by the tetracyclines, which produce effects on teeth and bones only after the third month of gestation, when mineralization begins.

b) *Transplacental passage.* Most drugs can pass in the placenta from the maternal into the fetal circulation. The syncytiotrophoblast formed by the fusion of cytotrophoblast cells represents the major diffusion barrier. It possesses a higher permeability to drugs than suggested by the term "placental barrier." Accordingly, all centrally acting drugs administered to a pregnant woman can easily reach the fetal organism. Relevant examples include antiepileptics, anxiolytics, hypnotics, antidepressants, and neuroleptics.

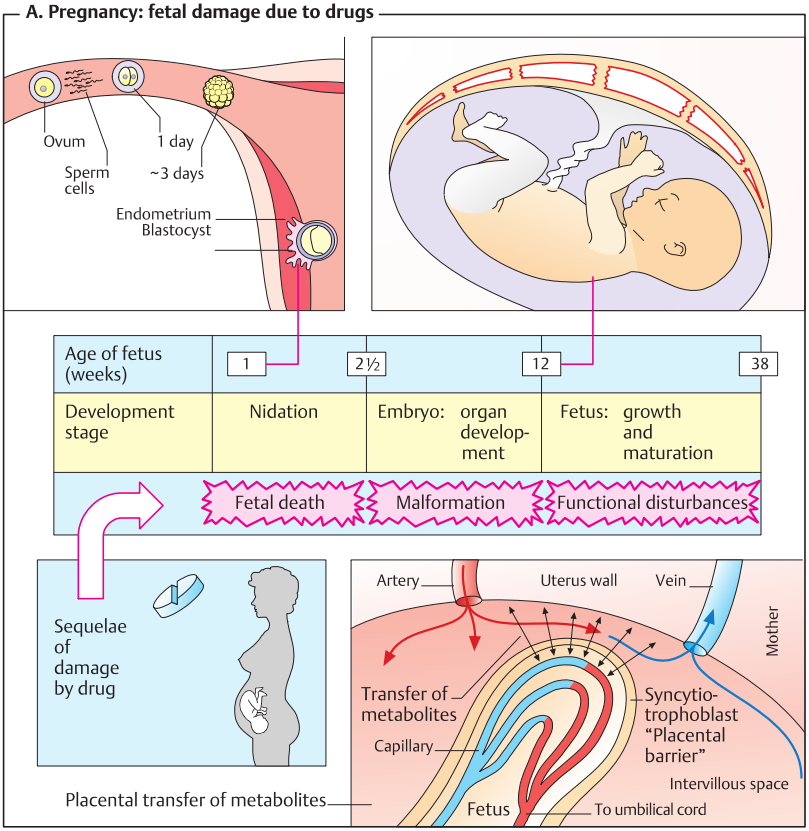
c) *Teratogenicity.* Statistical risk estimates are available for familiar, frequently used drugs. For many drugs, teratogenic potency cannot be demonstrated; however, in the case of novel drugs it is usually not yet possible to define their teratogenic hazard. To give an example: if it can be stated that a certain drug increases the risk of malformation by a factor of 5, what this means should be understood (and possibly explained to the mother-to-be): in healthy women, about one malformation occurs in 1000 births, that is, 999 children are born without a malformation. The increase by a factor of 5 means that in our example 995 children will be born healthy despite the risk due to the drug.

Drugs with established human teratogenicity include derivatives of vitamin A (etretinate, isotretinoic acid). A peculiar type of damage results from the synthetic estrogenic agent diethylstilbestrol following its use during pregnancy: daughters of treated mothers have an increased incidence of cervical and vaginal carcinoma at the age of about 20 years. Use of this substance in pregnancy was banned in the United States in 1971.

In assessing the risk–benefit ratio, it is also necessary to consider the benefit for the child resulting from adequate therapeutic treatment of its mother. For instance, therapy with antiepileptic drugs is indispensable, because untreated epilepsy endangers the unborn child at least as much as does administration of anticonvulsants.

Drug withdrawal reactions may occur in neonates whose mothers use drugs of abuse or antidepressants of the SSRI type.

► **Lactation** (► **Fig. 10.4B**). Drugs present in the maternal organism can be secreted in breast milk and thus be ingested by the infant. Evaluation of risks should be based on factors listed in ► Fig. 10.4**B**. In case of doubt, potential danger to the infant can be averted only by weaning.


A. Pregnancy: fetal damage due to drugs
Ovum
Sperm cells
1 day
~3 days
Endometrium
Blastocyst
Age of fetus (weeks)
1
2½
12
38
Development stage
Nidation
Embryo: organ development
Fetus: growth and maturation
Fetal death
Malformation
Functional disturbances
Sequelae of damage by drug
Placental transfer of metabolites
Artery
Uterus wall
Vein
Mother
Transfer of metabolites
Capillary
Syncytio-trophoblast "Placental barrier"
Intervillous space
Fetus
To umbilical cord

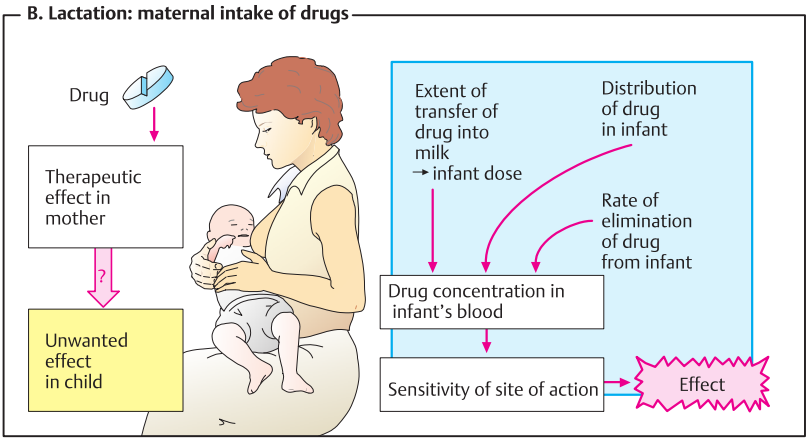

B. Lactation: maternal intake of drugs
Drug
Therapeutic effect in mother
?
Unwanted effect in child
Extent of transfer of drug into milk → infant dose
Distribution of drug in infant
Rate of elimination of drug from infant
Drug concentration in infant's blood
Sensitivity of site of action
Effect

Fig. 10.4

Pharmacogenetics

Pharmacogenetics is concerned with the genetic variability of drug effects. Differences in genetic sequences that occur at a frequency of at least 1% are designated as **polymorphisms**. **Rare variants** are observed in less than 1% of a population. Polymorphisms may either influence the pharmacokinetics of a drug or occur in the genes that code the proteins for drug binding and drug action. Genetic variants can arise in the germline (genes) and therefore be present in all cells in the body (▶ Fig. 10.5A). They can also occur selectively, however, as "somatic mutations" in individual cells, for instance contributing to the development of tumors (▶ Fig. 10.5A). Body cells or tumor material must be tested genetically depending on whether germline or somatic mutations are present.

▶ **Genetic variants of pharmacokinetics.** Polymorphisms can occur in all genes that participate in the absorption, distribution, biotransformation, and elimination of drugs. Subjects who break down a drug more slowly owing to a genetic defect are classified as "slow metabolizers" or "poor metabolizers" in contrast to "normal metabolizers." When delayed biotransformation causes an excessive rise in plasma levels, the incidence of toxic effects increases, as evidenced by the example of the immunosuppressants azathioprine and mercaptopurine. Both substances are converted to inactive methylthiopurines by the enzyme **thiopurine methyltransferase** (TMPT). About 10% of patients carry a genetic polymorphism that leads to reduced TMPT activity and in < 1% enzyme activity is undetectable. As a result of the diminished purine methylation, the plasma level of active drug rises and, hence, the risk of toxic bone marrow damage rises. To avoid unwanted toxic effects, TMPT activity can be determined in erythrocytes before therapy with mercaptopurine is started. In patients with complete TMPT deficiency, the dose of azathioprine should be reduced by 90%.

Other genetic variants of drug metabolism may have a similar impact: a defect of ***N*-acetyltransferase 2** impedes the N-acetylation of diverse drugs, including isoniazid, hydralazine, sulfonamides, clonazepam, and nitrazepam. "Slow acetylators" (50–60% of the population) are more likely than "fast acetylators" to develop toxic reactions and neuropathy. A genetic defect of the **cytochrome P450 isozyme CYP2D6** (originally described as debrisoquine–sparteine polymorphism) occurs in ~8% of Europeans and results in delayed elimination of various drugs, including metoprolol, flecainide, nortriptyline, desipramine, and amitriptyline. CYP2D6 variants influence not only drug inactivation but also activation. For instance, the plasma level of endoxifen, the active metabolite of tamoxifen, depends on the activity of the CYP2D6 enzyme (p. 50).

▶ **Genetic variants of pharmacodynamics.** Genetic polymorphisms can also involve genes that mediate the effects of drugs and, hence, alter pharmacodynamics. In these cases, the biological effects of a drug are changed, rather than its plasma levels. Ivacaftor, which is licensed for treatment of mucoviscidosis (cystic fibrosis) patients with a certain genetic variant of the CFTR chloride channel (CFTR-G441D) provides an example. In this CFTR mutation, ivacaftor improves the defective opening of the chloride channel. Genetic variants can also be associated with an increased risk of adverse drug effects. For instance, severe hypersensitivity reactions to abacavir occur much more often in HIV patients with HLA-B*5701 genotype than in patients without this HLA variant, so they must not be given abacavir.

▶ **Genetic variants of pharmacodynamics in tumor cells.** Mutations in somatic genes can be very important for the response to tumor therapy. The kinase inhibitor imatinib (p. 302) works particularly well in cells in which the fusion protein Bcr-Abl has occurred due to genetic translocation. By contrast, panitumumab, an antibody directed against the EGF receptor (= HER1), is ineffective in such tumor cells, where activating mutations occur in the *KRAS* gene and promote cell proliferation (p. 300 and cf. Table 47.1).

A summary of the drugs for which genetic tests are useful or necessary can be found at www.pharmgkb.org.

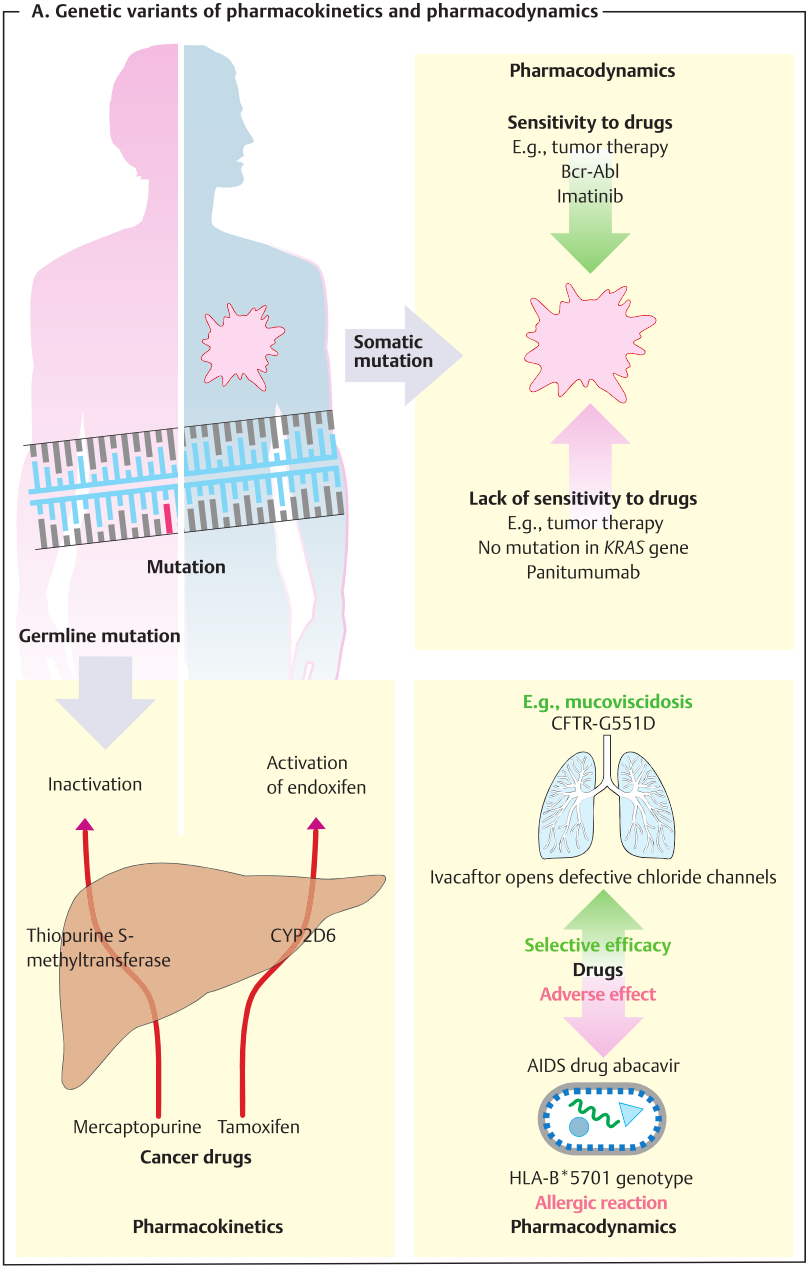

A. Genetic variants of pharmacokinetics and pharmacodynamics
Pharmacodynamics
Sensitivity to drugs
E.g., tumor therapy
Bcr-Abl
Imatinib
Somatic mutation
Lack of sensitivity to drugs
E.g., tumor therapy
No mutation in KRAS gene
Panitumumab
Mutation
Germline mutation
Inactivation
Activation of endoxifen
Thiopurine S-methyltransferase
CYP2D6
Mercaptopurine
Tamoxifen
Cancer drugs
Pharmacokinetics
E.g., mucoviscidosis
CFTR-G551D
Ivacaftor opens defective chloride channels
Selective efficacy
Drugs
Adverse effect
AIDS drug abacavir
HLA-B*5701 genotype
Allergic reaction
Pharmacodynamics

Fig. 10.5

Placebos and the Placebo Effect

A placebo (▶ Fig. 11.1**A**) is a dosage form devoid of an active ingredient—a dummy medication. Administration of a placebo may elicit the desired effect (relief of symptoms) or undesired effects that reflect a change in the patient's psychological situation brought about by the therapeutic setting.

Therapists may consciously or unconsciously communicate to the patient whether or not they are concerned about the patient's problem, or are certain about the diagnosis and about the value of prescribed therapeutic measures. In the care of a physician who projects personal warmth, competence, and confidence, the patient in turn feels comfort and less anxiety and optimistically anticipates recovery. The physical condition determines the psychic disposition and vice versa. Consider gravely wounded combatants in war, oblivious to their injuries while fighting to survive, only to experience severe pain in the safety of the field hospital; or the patient with a peptic ulcer caused by emotional stress.

▶ **Clinical trials.** In the individual case, it may be impossible to decide whether therapeutic success is attributable to the drug or to the therapeutic situation. What is therefore required is a comparison of the effects of a drug and of a placebo in matched groups of patients by means of statistical procedures, i.e., a placebo-controlled trial. For serious diseases, the comparison group has to be treated with the best therapy known to date, rather than a placebo. To be acceptable, the test group receiving the new medicine must show a result superior to that of the comparison group.

A prospective trial is planned in advance. A retrospective (case–control) study follows patients backward in time, the decision to analyze being made only after completion of therapy. Patients are randomly allotted to two groups, namely, the placebo and the active or test drug group. In a double-blind trial, neither the patients nor the treating physicians know which patient is given drug and which placebo. Finally, a switch from drug to placebo and vice versa can be made in a successive phase of treatment, the crossover trial. In this fashion, drug vs. placebo comparisons can be made not only between two patient groups but also within either group.

▶ **Homeopathy (▶ Fig. 11.1B).** Homeopathy is an alternative method of therapy, developed at the beginning of the 19th century by Samuel Hahnemann, which has taken no notice of the advances in medicine and science of the last 200 years. His idea was this: when given in normal (allopathic) dosage, a drug (in the sense of medicament) will produce a constellation of symptoms; however, in a patient whose disease symptoms resemble just this mosaic of symptoms, the same drug *(simile principle)* would effect a cure when given in a very low dosage *("potentiation")*. The body's self-healing powers were to be properly activated only by minimal doses of the medicinal substance. The homeopath's task is not to diagnose the causes of morbidity, but to find the drug with a "symptom profile" most closely resembling that of the patient's illness. This requires in-depth probing into the patient's complaints. With the accompaniment of a prescribed ("ritualized") shaking procedure, the drug is then highly diluted (in 10-fold or 100-fold series).

No direct action or effect on body functions can be demonstrated for homeopathic medicines. The suggestive power of a convinced homeopath undoubtedly contributes to the "therapeutic success" but also entails the danger that diseases that are curable by conventional (allopathic) medicine will not receive this treatment or that it will be employed too late. A salutary example that may be cited is the treatment of breast cancer with highly diluted mistletoe extract.

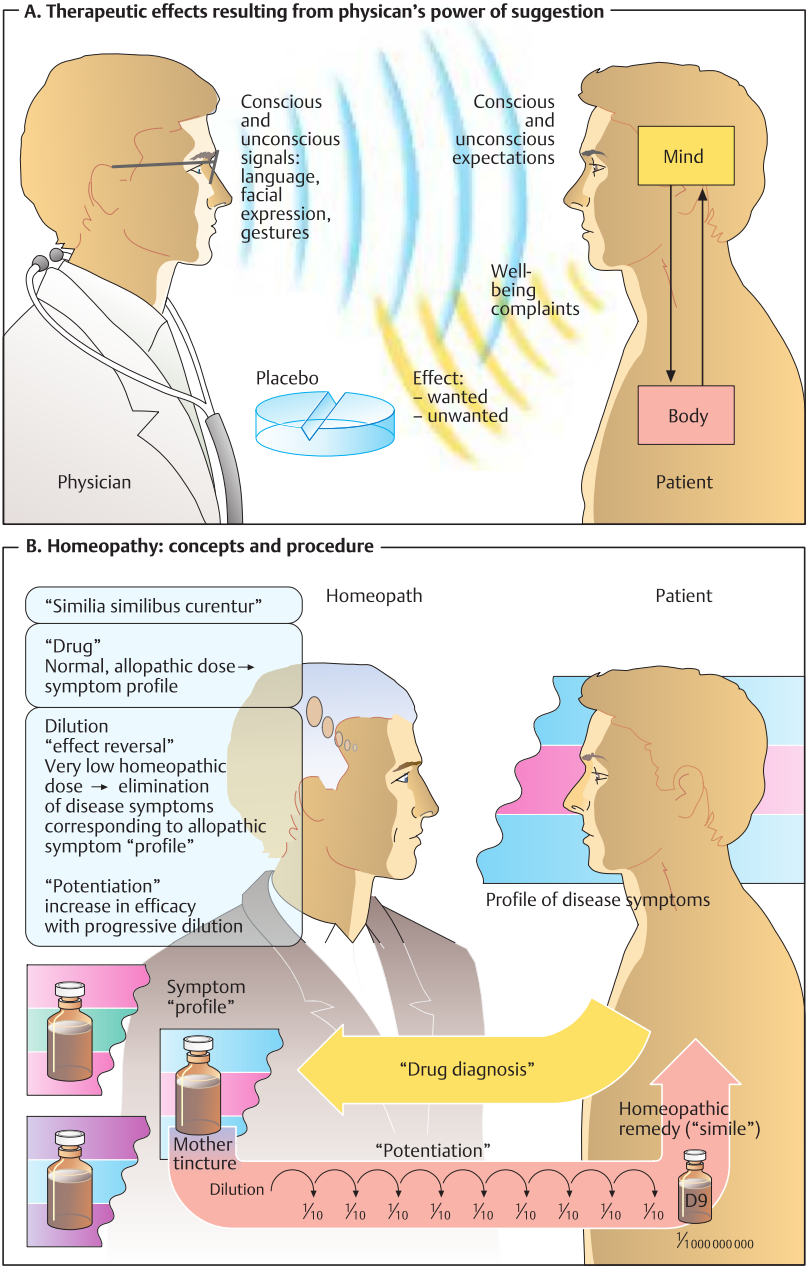

A. Therapeutic effects resulting from physican's power of suggestion
Conscious and unconscious signals: language, facial expression, gestures
Conscious and unconscious expectations
Mind
Well-being complaints
Placebo
Effect:
– wanted
– unwanted
Body
Physician
Patient
B. Homeopathy: concepts and procedure
"Similia similibus curentur"
Homeopath
Patient
"Drug"
Normal, allopathic dose → symptom profile
Dilution
"effect reversal"
Very low homeopathic dose → elimination of disease symptoms corresponding to allopathic symptom "profile"
"Potentiation"
increase in efficacy with progressive dilution
Profile of disease symptoms
Symptom "profile"
"Drug diagnosis"
Homeopathic remedy ("simile")
Mother tincture
"Potentiation"
Dilution
1/10 1/10 1/10 1/10 1/10 1/10 1/10 1/10 1/10
D9
1/1000 000 000

Fig. 11.1

Systems Pharmacology

Sympathetic Nervous System

In the course of phylogeny an efficient control system evolved that enabled the functions of individual organs to be orchestrated in increasingly complex life forms and permitted rapid adaptation to changing environmental conditions. This regulatory system consists of the central nervous system (CNS) (brain plus spinal cord) and two separate pathways for two-way communication with peripheral organs, namely, the somatic and the autonomic nervous systems. The **somatic nervous system**, comprising exteroceptive and interoceptive afferents, special sense organs, and motor efferents, serves to perceive *external* states and to target appropriate body movement (sensory perception: threat → response: flight or attack). The **autonomic** (**vegetative**) **nervous system** (ANS) together with the endocrine system controls the *milieu interieur*. It adjusts internal organ functions to the changing needs of the organism. Neural control permits very quick adaptation, whereas the endocrine system provides for long-term regulation of functional states. The ANS operates largely beyond voluntary control: it functions autonomously. Its central components reside in the hypothalamus, brainstem, and spinal cord. The ANS also participates in the regulation of endocrine functions.

The ANS has **sympathetic** and **parasympathetic** (p. 118) branches. Both are made up of centrifugal (efferent) and centripetal (afferent) nerves. In many organs innervated by both branches, respective activation of the sympathetic and parasympathetic input evokes opposing responses.

In various disease states (organ malfunctions), drugs are employed with the intention of normalizing susceptible organ functions. To understand the biological effects of substances capable of inhibiting or exciting sympathetic or parasympathetic nerves, one must first envisage the functions subserved by the sympathetic and parasympathetic divisions (▶ Fig. 12.1**A**, Response to sympathetic activation). In simplistic terms, activation of the sympathetic division can be considered a means by which the body achieves a state of maximal work capacity as required in fight-or-flight situations.

In both cases, there is a need for vigorous activity of skeletal musculature. To ensure adequate supply of oxygen and nutrients, blood flow in skeletal muscle is increased; cardiac rate and contractility are enhanced, resulting in a larger blood volume being pumped into the circulation. Narrowing of splanchnic blood vessels diverts blood into vascular beds in muscle.

Because digestion of food in the intestinal tract is dispensable and essentially counterproductive, the propulsion of intestinal contents is slowed to the extent that peristalsis diminishes and sphincters are narrowed. However, in order to increase nutrient supply to heart and musculature, glucose from the liver and free fatty acids from adipose tissue must be released into the blood. The bronchi are dilated, enabling tidal volume and alveolar oxygen uptake to be increased.

Sweat glands are also innervated by sympathetic fibers (wet palms due to excitement); however, these are exceptional as regards their neurotransmitter (ACh) (p. 126).

The lifestyles of modern humans are different from those of our hominid ancestors, but biological functions have remained the same: a "stress"-induced state of maximal work capacity, albeit without energy-consuming muscle activity. The various biological functions of the sympathetic nervous system are mediated by different receptors in the plasma membrane of the target cells into the interior of the cell. These receptors will be presented in detail in the following pages. To simplify the subsequent overview, the receptor subtypes involved in sympathetic responses are listed in ▶ Fig. 12.1**A** (α_1, α_2, β_1, β_2, β_3).

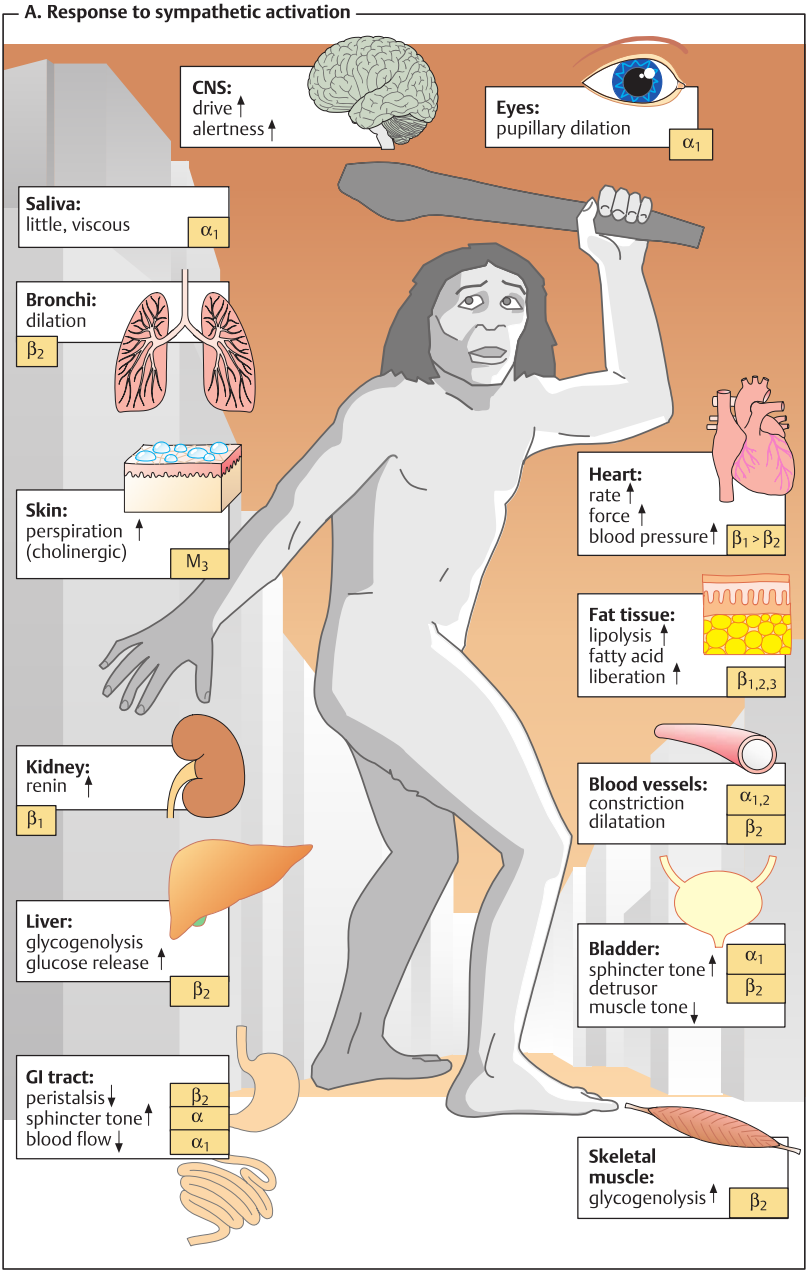

A. Response to sympathetic activation
CNS:
drive ↑
alertness ↑
Eyes:
pupillary dilation
α1
Saliva:
little, viscous
α1
Bronchi:
dilation
β2
Skin:
perspiration ↑
(cholinergic)
M3
Heart:
rate ↑
force ↑
blood pressure ↑
β1 > β2
Fat tissue:
lipolysis ↑
fatty acid
liberation ↑
β1,2,3
Kidney:
renin ↑
β1
Blood vessels:
constriction
dilatation
α1,2
β2
Liver:
glycogenolysis
glucose release ↑
β2
Bladder:
sphincter tone ↑
detrusor
muscle tone ↓
α1
β2
GI tract:
peristalsis ↓
sphincter tone ↑
blood flow ↓
β2
α
α1
Skeletal
muscle:
glycogenolysis ↑
β2

Fig. 12.1

Structure of the Sympathetic Nervous System

The sympathetic preganglionic neurons (first neurons) project from the intermediolateral column of the spinal gray matter to the *paired paravertebral ganglionic chain* lying alongside the vertebral column and to *unpaired prevertebral ganglia.* These **ganglia** represent sites of synaptic contact between **preganglionic axons** (1st neurons) and **nerve cells** (2nd neurons or sympathocytes, ▶ Fig. 12.2**A**) that emit axons terminating at **postganglionic synapses** (or contacts) on cells in various end organs. In addition, there are preganglionic neurons that project either to peripheral ganglia in end organs or to the adrenal medulla.

▶ **Sympathetic transmitter substances.** Whereas **acetylcholine** (see p. 120) serves as the chemical transmitter at ganglionic synapses between **first and second neurons**, **norepinephrine** (noradrenaline) is the mediator at synapses of the second neuron (▶ Fig. 12.2**A**). This second neuron does not synapse with only a single cell in the effector organ; rather it branches out, each branch making *en passant* contacts with several cells. At these junctions the nerve axons form enlargements (**varicosities**) resembling beads on a string. Thus, excitation of the neuron leads to activation of a larger aggregate of effector cells, although the action of released norepinephrine may be confined to the region of each junction. Excitation of preganglionic neurons innervating the adrenal medulla causes liberation of acetylcholine. This, in turn, elicits secretion of **epinephrine** (adrenaline) into the blood, by which it is distributed to body tissues as a hormone (▶ Fig. 12.2**A**).

Adrenergic Synapse

Within the varicosities, norepinephrine is stored in small membrane-enclosed vesicles (▶ Fig. 12.2**B**) (granules, 0.05–0.2 µm in diameter). In the axoplasm, norepinephrine is formed by stepwise enzymatic synthesis from L-tyrosine, which is converted by tyrosine hydroxylase (TH) to L-dopa (see Parkinson chapter, p. 334). L-dopa in turn is decarboxylated by aromatic amino acid decarboxylase (AADC) to dopamine, which is taken up into storage vesicles by the vesicular monoamine transporter (VMAT). In the vesicle, dopamine is converted to norepinephrine by dopamine β-hydroxylase (DBH). In the adrenal medulla, the major portion of norepinephrine undergoes enzymatic methylation to epinephrine by phenylethanolamine *N*-methyltransferase, PNMT.

When stimulated electrically, the sympathetic nerve discharges the contents of part of its vesicles, including norepinephrine, into the extracellular space. Liberated **norepinephrine** reacts with **adrenoceptors** located postjunctionally on the membrane of effector cells or prejunctionally on the membrane of varicosities. Activation of presynaptic α_2-receptors inhibits norepinephrine release. Through this negative feedback, release can be regulated.

The effect of released norepinephrine wanes quickly, because ~90% is transported back into the axoplasm by a specific transport mechanism (norepinephrine transporter, NET) and then into storage vesicles by the vesicular transporter (neuronal reuptake). The NET can be inhibited by tricyclic antidepressants, selective norepinephrine reuptake inhibitors (SNRIs), and cocaine. Moreover, norepinephrine is taken up by transporters into the effector cells (extraneuronal monoamine transporter, EMT). Part of the norepinephrine undergoing reuptake is enzymatically inactivated to normetanephrine via **c**atechol ***O*-m**ethyl**t**ransferase (COMT, present in the cytoplasm of postjunctional cells) and to dihydroxymandelic acid via **m**ono**a**mine **o**xidase (MAO, present in mitochondria of nerve cells and postjunctional cells).

Apart from the sympathetic nervous system, norepinephrine, epinephrine, and their receptors are also present in CNS neurons, e.g., in the locus ceruleus.

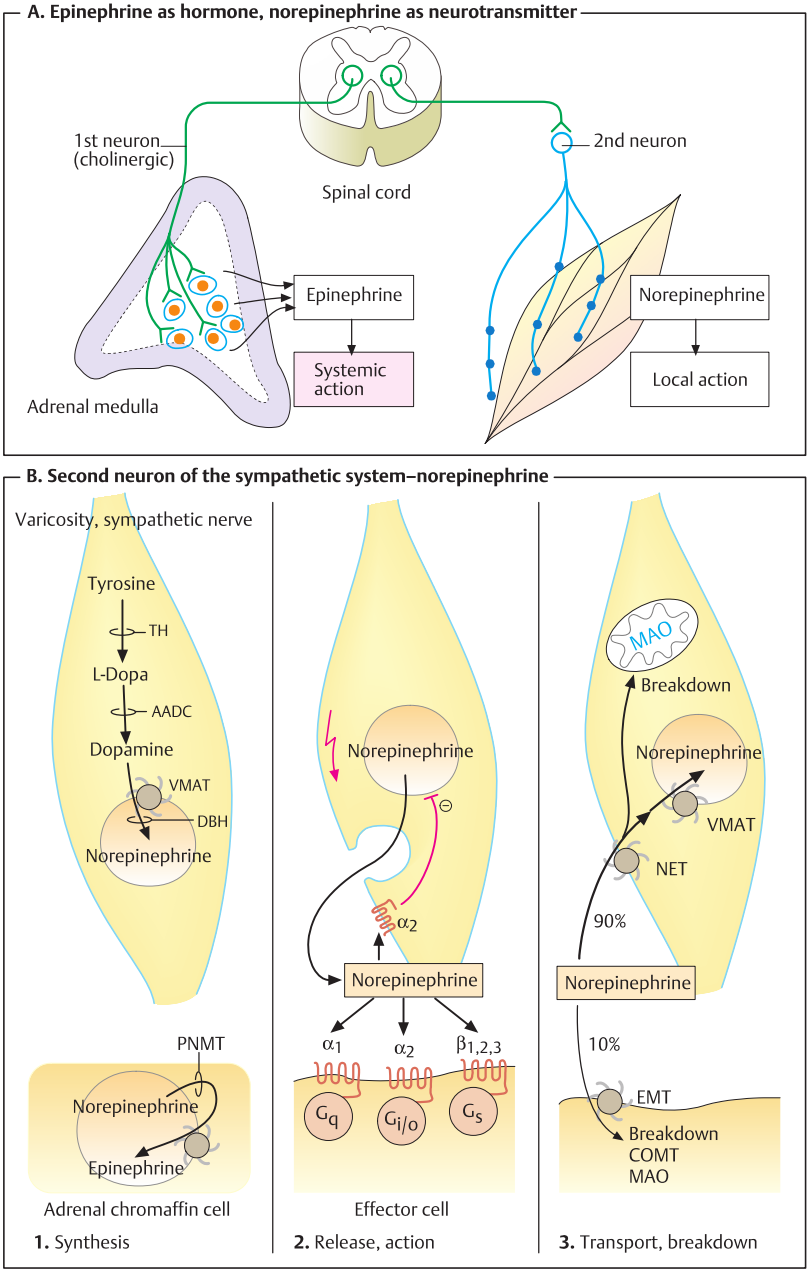

A. Epinephrine as hormone, norepinephrine as neurotransmitter
1st neuron (cholinergic)
Spinal cord
2nd neuron
Epinephrine
Systemic action
Adrenal medulla
Norepinephrine
Local action
B. Second neuron of the sympathetic system–norepinephrine
Varicosity, sympathetic nerve
Tyrosine
TH
L-Dopa
AADC
Dopamine
VMAT
DBH
Norepinephrine
PNMT
Norepinephrine
Epinephrine
Adrenal chromaffin cell
1. Synthesis
Norepinephrine
α2
Norepinephrine
α1
α2
β1,2,3
Gq
Gi/o
Gs
Effector cell
2. Release, action
MAO
Breakdown
Norepinephrine
VMAT
NET
90%
Norepinephrine
10%
EMT
Breakdown
COMT
MAO
3. Transport, breakdown

Fig. 12.2

Adrenoceptor Subtypes and Catecholamine Actions

The biological effects of epinephrine and norepinephrine are mediated by nine different adrenoceptors ($\alpha_{1A,B,D}$, $\alpha_{2A,B,C}$, β_1, β_2, β_3). To date, only the classification into α_1, α_2, β_1, β_2, and β_3-receptors has therapeutic relevance. Adrenoceptor agonists are used for various indications.

Smooth Muscle Effects

The effects on smooth muscle (▶ Fig. 12.3**A**) of α- and β-adrenoceptor activation are due to differences in signal transduction. α_1-Receptor stimulation leads to activation of phospholipase C via $G_{q/11}$ proteins with subsequent production of the intracellular messenger inositol triphosphate (IP_3) and increased intracellular release of calcium ions. In concert with the protein calmodulin, Ca^{2+} can activate myosin light chain kinase, leading to a rise in smooth muscle tone via phosphorylation of the contractile protein myosin → vasoconstriction). α_2-Adrenoceptors can also elicit a contraction of smooth muscle cells by activating phospholipase C (PLC) via the βγ-subunits of G_i proteins.

cAMP inhibits activation of myosin light chain kinase. Via stimulatory G-proteins (G_s), β_2-receptors mediate an increase in cAMP production (→ vasodilation). Subsequent inhibition of myosin light chain kinase leads to relaxation of smooth muscle cells.

▶ **Vasoconstriction and vasodilatation.** Vasoconstriction induced by local administration of α-sympathomimetics can be employed in infiltration anesthesia or for nasal decongestion (naphazoline, tetrahydrozoline, xylometazoline). Systemically administered epinephrine is important to increase blood pressure in the treatment of anaphylactic shock and cardiac arrest. α_1-Adrenoceptor antagonists are employed in the treatment of essential hypertension and benign prostatic hypertrophy.

▶ **Bronchodilation.** β_2-Adrenoceptor-mediated *bronchodilation* (e.g., by fenoterol, salbutamol, and terbutaline) plays an essential part in the treatment of bronchial asthma and chronic obstructive lung disease (p. 358). For this purpose, β_2-agonists are usually given by inhalation; preferred agents being those with low oral bioavailability and low risk of systemic unwanted effects (e.g., fenoterol, salbutamol, terbutaline). Rapid- and short-acting substances such as salbutamol or fenoterol are used to treat acute bronchospasm. Long-acting inhaled β_2-mimetic agents are available for prevention, for instance, salmeterol and formoterol (each with a duration of action of about 12 h), and indacaterol, olaterol and vilaterol (duration of action roughly 24 h).

▶ **Tocolysis.** The uterine relaxant effect of β_2-adrenoceptor agonists, such as fenoterol, can be used to prevent *premature labor*. β_2-Vasodilatation in the mother with an imminent drop in systemic blood pressure results in reflex tachycardia, which is also due in part to the β_1-stimulant action of these drugs. More prolonged β_2-receptor stimulation by tocolytic agents leads to a drop in efficacy, necessitating an increase in dose (see Receptor desensitization, p. 108).

▶ **Overactive bladder.** The relaxant effect of β_3-receptor activation can be used to reduce excessive bladder wall tone and urge incontinence with the β_3-agonist mirabegron.

Cardiostimulation

By stimulating β-receptors, and hence **cAMP** production, catecholamines augment all heart functions including systolic force (positive inotropic effect), velocity of myocyte shortening, sinoatrial rate (positive chronotropic effect), conduction velocity (dromotropic effect), and excitability (bathmotropic effect). In pacemaker fibers, cAMP-gated channels ("pacemaker channels") are activated, whereby *diastolic depolarization* is hastened and the firing threshold for the action potential is reached sooner (▶ Fig. 12.3**B**). cAMP activates protein kinase A, which phosphorylates different Ca^{2+} transport proteins. In this way, contraction of heart muscle cells is accelerated, as more Ca^{2+} enters the cell from the extracellular space via L-type Ca^{2+} channels and release of Ca^{2+} from the sarcoplasmic reticulum (via ryanodine receptors, RyR) is augmented. Faster relaxation of heart muscle cells is effected by phosphorylation of troponin and phospholamban (reduced inhibition of Ca^{2+}-ATPase).

In acute heart failure or cardiac arrest, β-mimetics are used as a short-term emergency measure; in chronic failure they are not indicated.

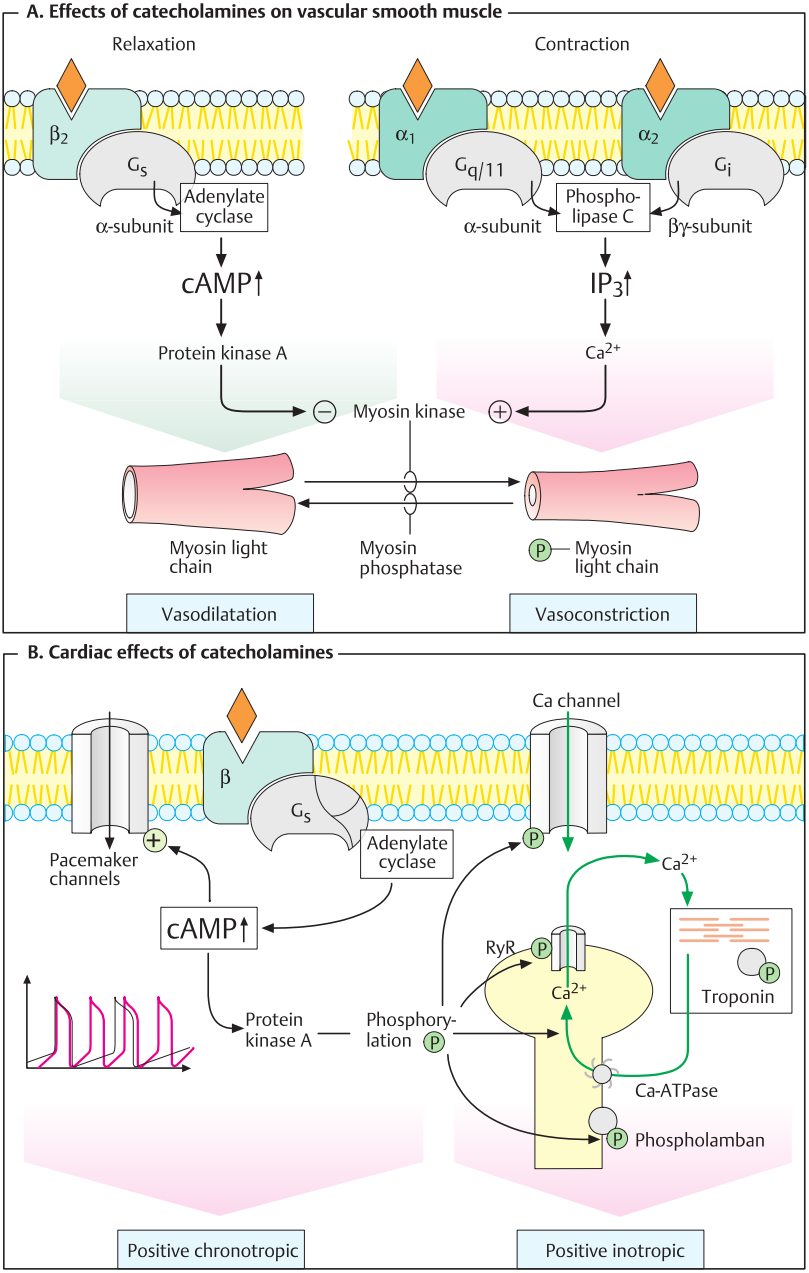

A. Effects of catecholamines on vascular smooth muscle
Relaxation
Contraction
β2
Gs
Adenylate cyclase
α-subunit
α1
Gq/11
α2
Gi
Phospho-lipase C
α-subunit
βγ-subunit
cAMP↑
IP3↑
Protein kinase A
Ca2+
Myosin kinase
Myosin light chain
Myosin phosphatase
P
Myosin light chain
Vasodilatation
Vasoconstriction
B. Cardiac effects of catecholamines
Ca channel
β
Gs
Adenylate cyclase
Pacemaker channels
cAMP↑
Protein kinase A
Phosphory-lation
P
RyR
Ca2+
Ca2+
Troponin
Ca-ATPase
Phospholamban
Positive chronotropic
Positive inotropic

Fig. 12.3

Metabolic Effects

β_1-Receptors via cAMP and α_1-receptors via $G_{q/11}$ signaling pathways mediate increased conversion of glycogen to glucose *(glycogenolysis)* (▶ Fig. 12.4**A**) in both liver and skeletal muscle. From the liver, glucose is released into the blood. In adipose tissue, triglycerides are hydrolyzed to fatty acids *(lipolysis* mediated by β_2- and β_3-receptors), which then enter the blood.

Receptor Desensitization

Prolonged agonist stimulation activates cellular processes that lead to partial switching off ("desensitization") of the receptor signal (▶ Fig. 12.4**B**). Within seconds after receptor activation, kinases (e.g., protein kinase A, G-protein-coupled receptor kinases, GRK) are stimulated; these phosphorylate intracellular receptor domains, thereby decoupling the receptor and G-protein. Phosphorylated receptors are recognized by the adapter protein arrestin, which initiates endocytosis of the receptors within minutes. Receptors can also activate intracellular signaling pathways via arrestin independent of G-protein stimulation. Individual receptor ligands and drugs that switch on G-proteins or arrestins selectively ("biased signaling") have been identified but the therapeutic significance of this effect is still unknown. Receptors on the cell surface are removed by endocytosis and taken up into endosomes. From here the receptors can either be transported onward to lysosomes to be broken down or they can return to the plasma membrane ("recycling"), where they are ready for further signal transmission. Prolonged receptor activation (hours) also reduces synthesis of new receptor proteins by influencing transcription, RNA stability, and translation. Overall, these processes protect the cell against overstimulation, but they also reduce the effect of agonists employed as drugs. When an agonist is given continuously or repeatedly, the effects achieved diminish (tachyphylaxis). When β_2-mimetics are infused to inhibit premature labor, the tocolytic effect falls steadily. This process can usually be counteracted by increasing the drug dose for only a short time until the increasing tachycardia due to activation of cardiac β-receptors limits further dose increases.

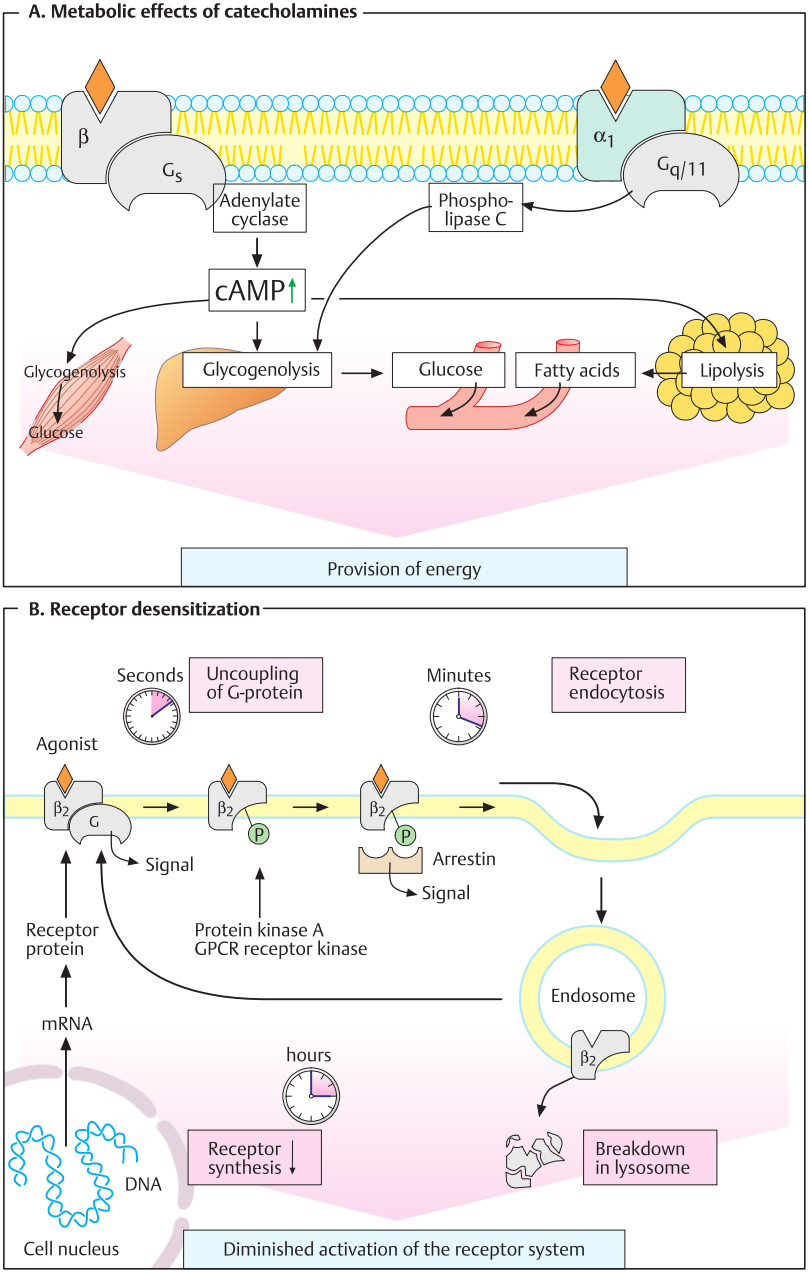

A. Metabolic effects of catecholamines
β
G_s
Adenylate cyclase
α_1
$G_{q/11}$
Phospho-lipase C
cAMP↑
Glycogenolysis
Glucose
Glycogenolysis
Glucose
Fatty acids
Lipolysis
Provision of energy
B. Receptor desensitization
Seconds
Uncoupling of G-protein
Minutes
Receptor endocytosis
Agonist
β_2
G
Signal
P
Arrestin
Signal
Receptor protein
Protein kinase A
GPCR receptor kinase
Endosome
mRNA
hours
DNA
Receptor synthesis ↓
Breakdown in lysosome
Cell nucleus
Diminished activation of the receptor system

Fig. 12.4

Structure–Activity Relationships of Sympathomimetics

► **Three-dimensional structure of the adrenoceptors** (► **Fig. 12.5A**). Adrenoceptors belong to the G-protein-coupled receptor class. These have seven transmembrane helices and are located in the plasma membrane. With the purification and crystallization of β_2-adrenoceptors, the three-dimensional structure of these receptors was first decoded in 2007 (► Fig. 12.5**A**). Brian K. Kobilka and Robert J. Lefkowitz (USA) were awarded the Nobel Prize in Chemistry in 2012 for discovering adrenoceptor structure and function. Similarly to rhodopsin, the transmembrane domains of the receptor (light brown) are arranged in a circle to produce a binding pocket for ligands (epinephrine, white) in the center. Epinephrine causes a conformational change in the receptor, which is transmitted to a G-protein on the inside of the membrane.

Epinephrine is specifically recognized by the receptor through several interaction sites (catechol OH groups, α-OH group, amino group, aromatic ring) (► Fig. 12.5**B**). If these interaction groups are absent, affinity for the receptor diminishes, but a few substances can still be recognized and transported by the transporters of the adrenergic system so that "indirect sympathomimetics" are produced, e.g., amphetamine(p. 112).

Owing to its equally high affinity for all α- and β-receptors, epinephrine does not permit selective activation of a particular receptor subtype. Like most catecholamines, it is also unsuitable for oral administration (catechol is a common name for *o*-hydroxyphenol). Norepinephrine differs from epinephrine by its high affinity for α-receptors and low affinity for β_2-receptors. The converse holds true for the synthetic substance, isoproterenol (isoprenaline) (► Fig. 12.5**A**).

Norepinephrine → α_1, β_1
Epinephrine → α, β_1, β_2
Isoproterenol → β_1, β_2

Knowledge of **structure–activity relationships** has permitted the synthesis of sympathomimetics that display a high degree of selectivity at adrenoceptor subtypes.

Direct-acting sympathomimetics (**C**) (i.e., adrenoceptor agonists) typically share a *phenethylamine* structure. The *side chain β-hydroxyl group* confers affinity for α- and β-receptors. *Substitution on the amino group* reduces affinity for α-receptors, but increases it for β-receptors (exception: α-agonist phenylephrine), with optimal affinity being seen after the introduction of only one isopropyl group. Increasing the bulk of amino substituents favors affinity for β_2-receptors (e.g., fenoterol, salbutamol). Both *hydroxyl groups* on the aromatic nucleus contribute to affinity; high activity at α-receptors is associated with hydroxyl groups at the 3 and 4 positions. Affinity for β-receptors is preserved in congeners bearing hydroxyl groups at positions 3 and 5 (orciprenaline, terbutaline, fenoterol).

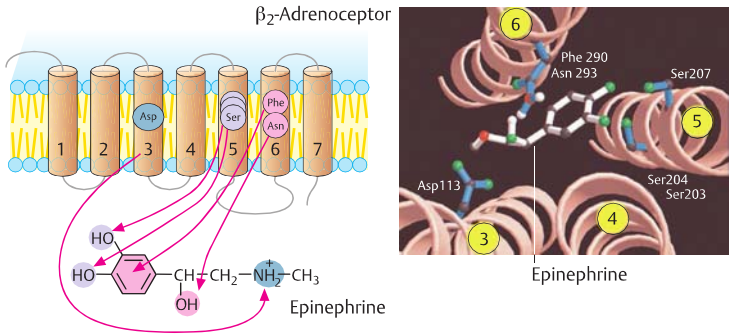
The hydroxyl groups of catecholamines are responsible for the very low lipophilicity of these substances. Polarity is increased at physiological pH owing to protonation of the amino group. Deletion of one or all hydroxyl groups improves the membrane penetrability at the intestinal mucosa–blood barrier and the blood–brain barrier. Accordingly, these noncatecholamine congeners can be given orally and can exert CNS actions; however, this structural change entails a loss in affinity.

Absence of one or both hydroxyl groups is associated with an increase in **indirect sympathomimetic activity** (p. 112), denoting the ability of a substance to release norepinephrine from its neuronal stores without exerting an agonist action at the adrenoceptor.

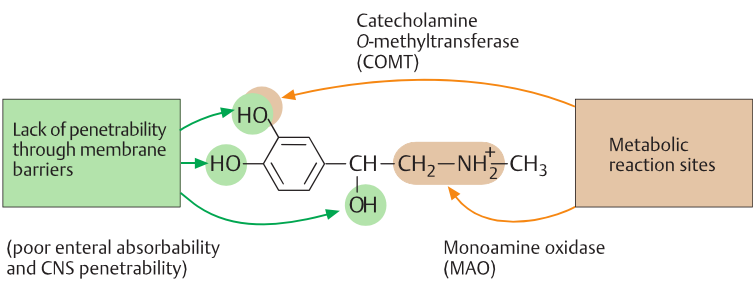
A change in position of the hydroxyl groups (e.g., in orciprenaline, fenoterol, or terbutaline) or their substitution (e.g., salbutamol) protects against *inactivation by COMT*. Introduction of a small alkyl residue at the carbon atom adjacent to the amino group (ephedrine, methamphetamine) confers resistance to *degradation by MAO;* replacement on the amino groups of the methyl residue with larger substituents (e.g., ethyl in etilefrine) impedes deamination by MAO.

Since structural requirements for high affinity on the one hand and oral applicability on the other do not match, choosing a sympathomimetic is a matter of compromise. If the high affinity of epinephrine is to be exploited, absorbability from the intestine must be foregone (epinephrine, isoprenaline). If good bioavailability with oral administration is desired, losses in receptor affinity must be accepted (etilefrine).

A. Interaction between epinephrine and the β_2-adrenoceptor



B. Structure–activity relationship of epinephrine



C. Direct sympathomimetics

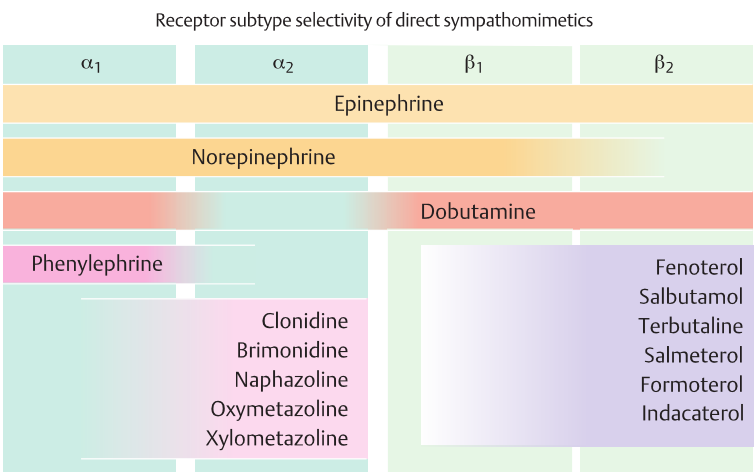


Fig. 12.5

Indirect Sympathomimetics

The concentration of norepinephrine in the synaptic space can be increased by:

- promoting the synaptic release of norepinephrine (▶ Fig. 12.6**A**)
- inhibiting the reuptake of norepinephrine into the nerve ending (▶ Fig. 12.6**A**)
- inhibiting breakdown by monoamine oxidase (MAO) or catechol *O*-methyltransferase (COMT) (▶ Fig. 12.6**B**).

Congeners of norepinephrine without catechol and hydroxyl OH groups lose their affinity for the adrenergic receptors but are still recognized as substrates by the transporters in the plasma membrane (NET) and vesicles (VMAT). These substances are called **indirect sympathomimetics** (iSM) in the narrower sense as they promote the release of norepinephrine over a nonexocytotic mechanism and thus trigger postsynaptic effects "indirectly" via adrenoceptors (▶ Fig. 12.6**A**). Indirect sympathomimetics are taken up into the axoplasm through presynaptic NETs. There they increase the concentration of norepinephrine in the cytosol by competing with norepinephrine for uptake into storage vesicles and breakdown by MAO. Phosphorylation at the amino terminal of NET appears to be the precondition for reversal of the transporter and nonexocytotic norepinephrine release. The effectiveness of the indirect sympathomimetics can diminish rapidly (**tachyphylaxis**).

Ephedrine is both a direct and an indirect sympathomimetic that is now used only in "cold remedies" (▶ Fig. 12.6**C**). Indirect sympathomimetics such as **amphetamine** can cross the blood–brain barrier and produce a feeling of well-being, enhanced physical activity, and elevated mood (euphoria); hunger and physical fatigue are lessened. Subsequent tiredness and depression are partly responsible for the urge to re-administer the drug (high abuse potential). The increased release of dopamine in the CNS is held responsible for the addictive effect of the amphetamines. In order to prevent misuse, these drugs are subject to governmental regulations.

The mentally stimulating effects are particularly marked in the case of the "designer drug" ecstasy, which contains **methylene dioxymethamphetamine** (MDMA). This derivative inhibits the reuptake not only of norepinephrine and dopamine but also of serotonin. Deaths are observed with overdose, and are due to extreme hyperthermia, seizures, and circulatory and renal failure.

Inhibitors of the norepinephrine transporter, which do not enter the axoplasm but only block norepinephrine reuptake, are employed as antidepressants, e.g., desipramine and reboxetine. **Methylphenidate**, which blocks the reuptake of norepinephrine and dopamine, causes effects similar to those of amphetamine. It is used in children to treat attention deficit hyperactivity disorder (ADHD). There has been much criticism of this use. Alternatives available for the treatment of ADHD are **modafinil** and **atomoxetine** (a direct NET inhibitor) as well as dexamphetamine and lisdexamfetamine.

Cocaine, the first local anesthetic, was long used in ophthalmology. It inhibits norepinephrine, dopamine, and serotonin transporters. The local anesthetic effect occurs only at high concentrations due to a blocking action on the Na^+ channel. Because of the high risk of addiction, it is used rarely in medicine today but it is highly popular in the "recreational drug scene."

Monoamine oxidase inhibitors block the MAO contained in the mitochondria, which keeps the norepinephrine concentration in the axoplasm low. MAO inhibition in the CNS affects the storage of dopamine and serotonin as well as of norepinephrine. This produces general activation and increased drive. **Moclobemide** is a reversible MAO_A inhibitor and is used as an antidepressant. The MAO_B inhibitor **selegiline** is used as an antiparkinsonian drug. The COMT inhibitor entacapone is also used in the treatment of Parkinson disease (p. 334).

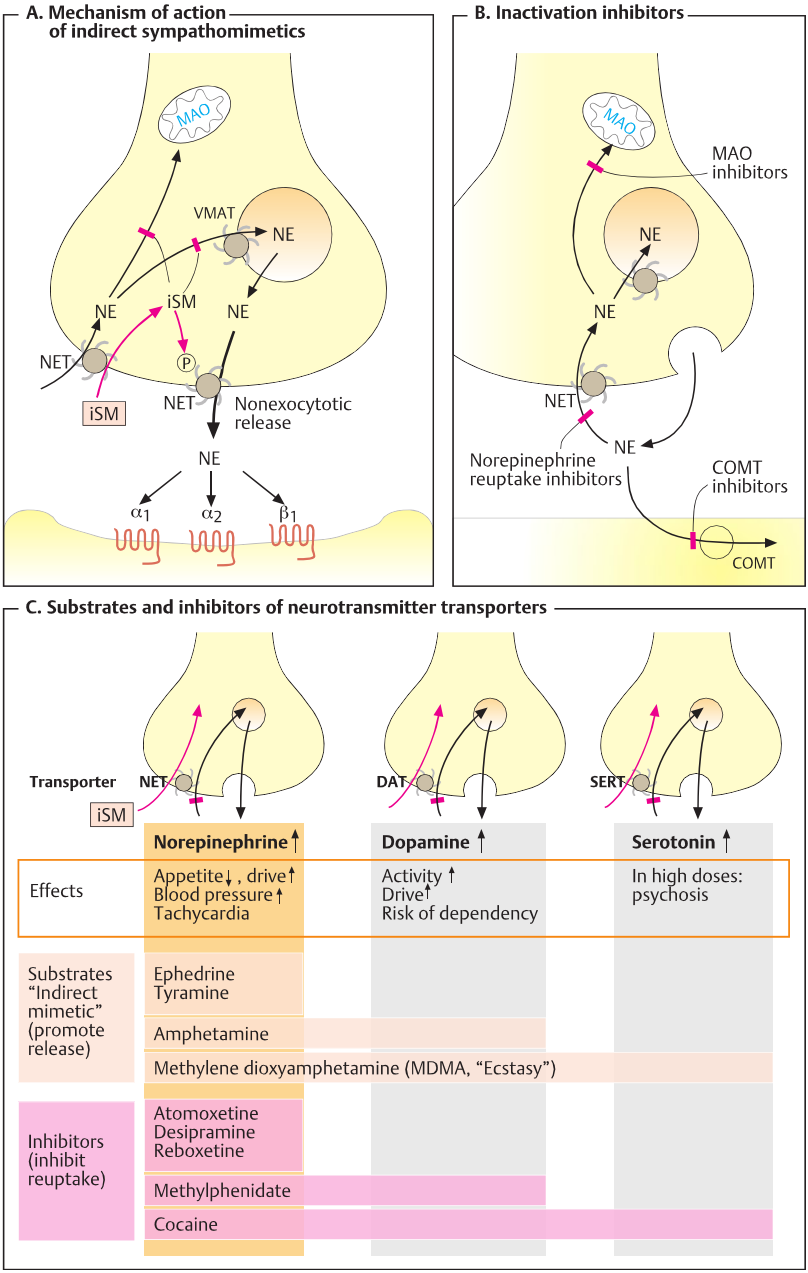

A. Mechanism of action of indirect sympathomimetics
MAO
VMAT
NE
NE
iSM
NE
NET
P
iSM
NET
Nonexocytotic release
NE
α1
α2
β1
B. Inactivation inhibitors
MAO
MAO inhibitors
NE
NE
NET
NE
Norepinephrine reuptake inhibitors
COMT inhibitors
COMT
C. Substrates and inhibitors of neurotransmitter transporters
Transporter
NET
DAT
SERT
iSM
Norepinephrine
Dopamine
Serotonin
Effects
Appetite↓, drive↑
Blood pressure↑
Tachycardia
Activity↑
Drive↑
Risk of dependency
In high doses: psychosis
Substrates "Indirect mimetic" (promote release)
Ephedrine
Tyramine
Amphetamine
Methylene dioxyamphetamine (MDMA, "Ecstasy")
Inhibitors (inhibit reuptake)
Atomoxetine
Desipramine
Reboxetine
Methylphenidate
Cocaine

Fig. 12.6

α-Sympathomimetics, α-Sympatholytics

Epinephrine and norepinephrine cause vasoconstriction and thus prolong the action of local anesthetics injected at the same time. Vasoconstriction induced by α-sympathomimetics is greater than the vasodilatation that can be produced by β-receptor activation. Drugs that stimulate only the α-receptors but not β-receptors are presented below.

α-Sympathomimetics

Clonidine is an α_2-agonist, which crosses the blood–brain barrier readily because of its high lipophilicity (dichlorophenyl ring) (▶ Fig. 12.7**A**). In the brainstem, clonidine modulates signals arriving from carotid artery and aortic arch baroreceptors so that when there is a rise in arterial blood pressure, the parasympathetic system is activated more and sympathetic tone falls. In addition, activation of peripheral presynaptic α_2-receptors leads to decreased release of norepinephrine from sympathetic nerves in the heart and blood vessels. Clonidine can thus effectively reduce blood pressure and heart rate. Apart from its principal use as an antihypertensive agent (especially in hypertensive crisis), clonidine can also be used in the treatment of opioid addiction to alleviate autonomic withdrawal symptoms. In addition, clonidine has a marked analgesic and sedative effect, which can be exploited in postoperative care. However, the sedation reduces clonidine's usefulness in the treatment of hypertension. The less sedating α_2-agonist moxonidine can be used in the treatment of high blood pressure. Clonidine derivatives (apraclonidine, brimonidine) reduce elevated intraocular pressure in glaucoma (see p. 346).

Dexmedetomidine (▶ Fig. 12.7**A**) is a specific, lipophilic α_2-sympathomimetic that penetrates the CNS well following intravenous injection. It can be used for sedation in the intensive care unit and during diagnostic procedures when waking the patient by verbal stimulation is permissible. Dexmedetomidine can cause hypotension and bradycardia by central sympathetic inhibition.

α-Sympathomimetics that penetrate the CNS less readily can be used as **topical** vasoconstrictors to reduce swelling of the nasal mucosa in coryza and to treat allergic or inflammatory conjunctivitis (▶ Fig. 12.7**B**); these include phenylephrine (α_1), xylometazoline (α_1, α_2), and oxymetazoline (α_1, α_2). As a result of the tissue hypoxia in the nasal mucosa, reactive hyperemia can occur after the vasoconstrictor effect subsides so that the patient applies the nasal drops repeatedly. Chronic use can lead to irreversible damage to the nasal mucosa. The use of decongestant nasal drops should be limited to 7–14 days at the most.

α-Sympatholytics

Activation of α-adrenoceptors by norepinephrine can be inhibited by α-adrenoceptor antagonists (α-sympatholytics) (▶ Fig. 12.7**C**). This can be put to therapeutic use in the management of hypertension and benign prostatic hypertrophy. The first α-sympatholytics blocked the action of norepinephrine not only at the postsynaptic α_1-receptors but also at the presynaptic α_2-receptors (nonspecific α-blockers, e.g., phenoxybenzamine, phentolamine).

Prazosin and the longer-acting α_1-antagonists doxazosin and terazosin are used as agents of second choice in hypertension (they do not reduce cardiovascular mortality, see p. 322). In patients with **benign prostatic hypertrophy**, they can reduce symptoms such as urgency and frequency by inhibiting α_1-receptors in the bladder neck and prostate. Alfuzosin, tamsulosin, and the structurally related silodosin, which have a higher affinity for the α_{1A}-receptors in the prostate, are licensed only for use in prostatic hypertrophy. Their hypotensive effects are said to be lower than those of doxazosin and terazosin. α_1-Blockers improve the symptoms of the disease but do not prevent further growth of the prostate. 5-α-Reductase inhibitors (e.g., finasteride, see p. 246) should be used to halt progression of the hypertrophy.

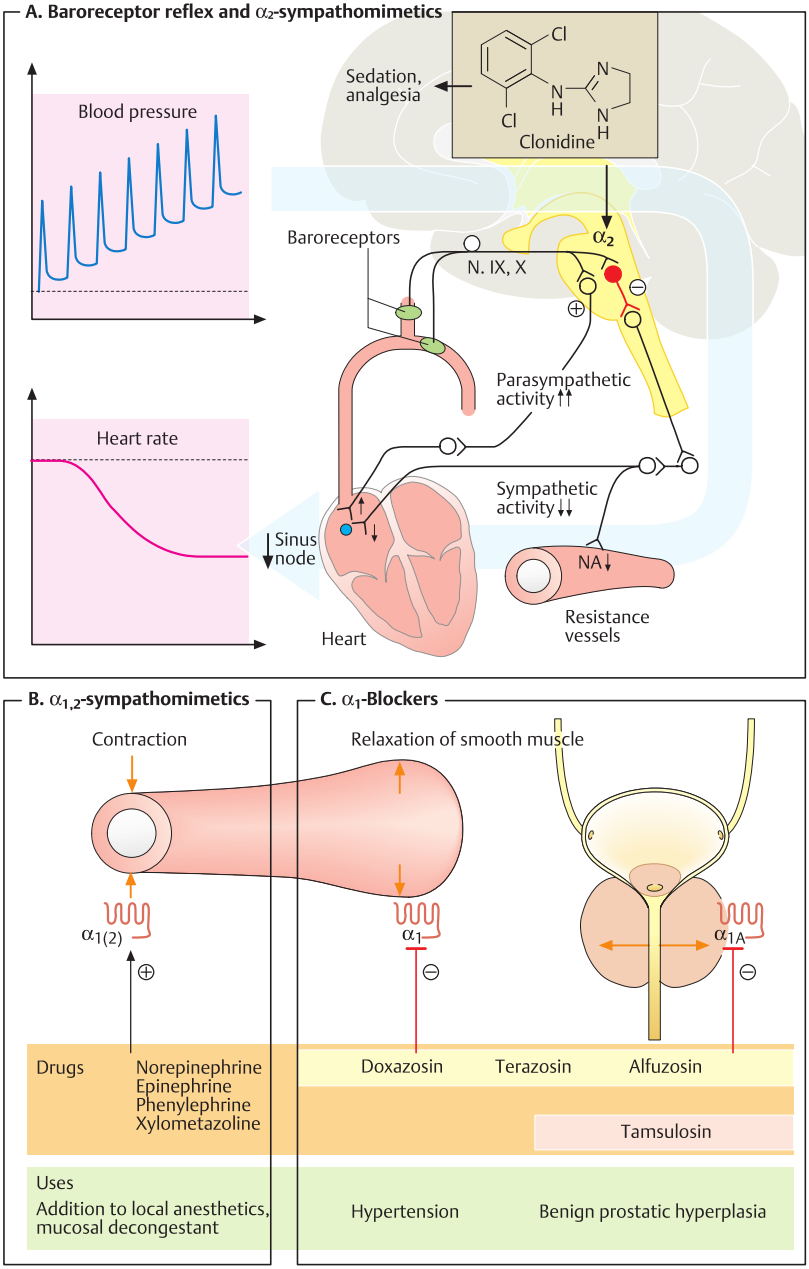

A. Baroreceptor reflex and α2-sympathomimetics
Blood pressure
Heart rate
Sedation, analgesia
Clonidine
Baroreceptors
N. IX, X
α2
Parasympathetic activity
Sympathetic activity
Sinus node
NA
Heart
Resistance vessels
B. α1,2-sympathomimetics
Contraction
α1(2)
C. α1-Blockers
Relaxation of smooth muscle
α1
α1A
Drugs
Norepinephrine
Epinephrine
Phenylephrine
Xylometazoline
Doxazosin
Terazosin
Alfuzosin
Tamsulosin
Uses
Addition to local anesthetics, mucosal decongestant
Hypertension
Benign prostatic hyperplasia

Fig. 12.7

β-Sympatholytics

β-Sympatholytics (β-blockers) are antagonists of norepinephrine and epinephrine at β-adrenoceptors and have no affinity for α-receptors. β-Blockers all share the basic chemical structure of the β-sympathomimetic side-chain (see p. 110) along with an aromatic substituent (▶ Fig. 12.8**A**). Propranolol was the first β-blocker to be used therapeutically in 1965 and about 25 chemically different β-blockers (analogue preparations) have been brought to market. Depending on their receptor affinity, the β-blockers can be classified as nonselective blockers (blocking both β_1- and β_2-receptors, e.g., **propranolol**) and selective β_1-antagonists (e.g., **metoprolol, bisoprolol, nebivolol, atenolol**). The β_1:β_2 selectivity factor is about 30 (–60) for most selective β_1-antagonists. This means that β_1-mediated effects are inhibited at a 30–60 times lower concentration (or dose) (green curve in **B**) than β_2-mediated effects (red curve). To give an example, ▶ Fig. 12.8**B** shows that when the plasma level range of a β_1-antagonist is in the therapeutic range, between 50% and 90% of the β_1-receptors have to be blocked in order, for example, to reduce the heart rate in a patient with CHD. At 30-fold selectivity, however, 3–25% of the β_2-receptors are occupied at the same plasma levels, and this can lead to side effects (see below).

The majority of the therapeutic effects of the β-blockers can be achieved by β_1-receptor blockade. Some β-blockers have other properties. **Carvedilol** also inhibits α_1-receptors and **nebivolol** is thought to have a vasodilating effect by causing NO release. Particular importance was formerly attributed to partial antagonists with intrinsic sympathomimetic activity (ISA). Today, ISA is regarded as a negative property of a β-blocker, at least in the treatment of heart failure.

▶ **Therapeutic effects (▶ Fig. 12.8C).** β-Blockers protect the heart against the oxygen-consuming effects of sympathetic stimulation by blocking β_1-receptors; thus, only a partial increase in cardiac work is possible (the heart is "coasting"). This effect is utilized in **coronary heart disease** in order to prevent stress on the heart that might trigger an angina attack. β-Blockers also serve to reduce the heart rate in **tachyarrhythmias** and protect the **failing heart** against excessive sympathetic drive. β-Blockers help to reduce blood pressure in **essential hypertension**: in addition to reducing the heart rate and cardiac contractility, they reduce central sympathetic tone and diminish β_1-receptor-mediated release of renin in the kidney.

β-Blockers are also used in the management of **glaucoma** (e.g., timolol, which reduces production of aqueous humor), prevention of **migraine**, and severe **hyperthyroidism** (sensitization of the myocardium to norepinephrine and epinephrine). Most of these pharmacological effects are achieved via β_1-receptors. In contrast, β_2-blockers may play an important part in the treatment of essential **tremor**.

▶ **Adverse effects (▶ Fig. 12.8C).** Side effects are due mainly to β_2-blocker effects. In patients with bronchial asthma or COPD, β_2-receptor blockade can cause bronchospasm with severe and life-threatening dyspnea (contraindication). In diabetics taking β-blockers, the warning symptoms of hypoglycemia (tachycardia, tremor) may be masked and the release of glucose from the liver induced by epinephrine is delayed. In addition, vascular β-receptor block leads to vasoconstriction with cold hands and feet and chronic circulatory disorders. Undesirable effects due to inhibition of β_1-receptors are bradycardia, hypotension, and AV block. In addition, β-blockers can cause headaches, depressed mood, and impotence.

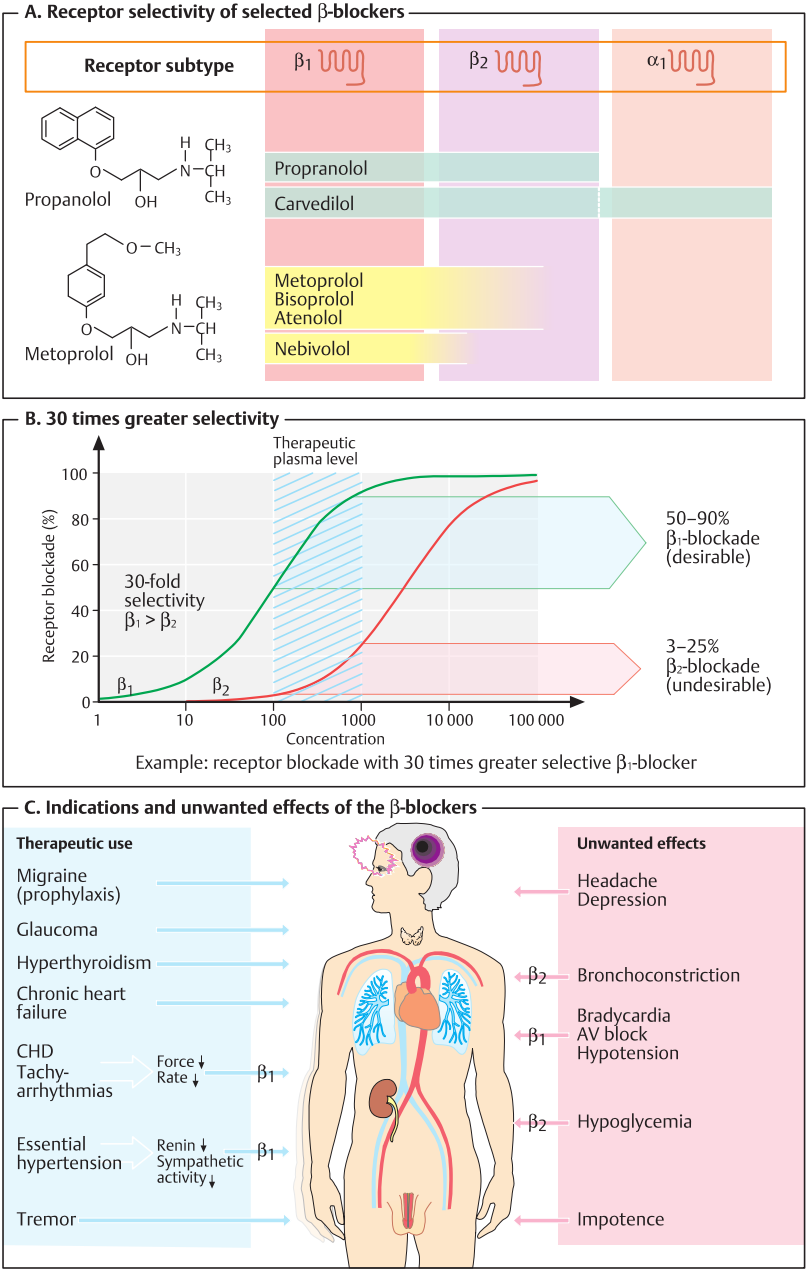

A. Receptor selectivity of selected β-blockers
Receptor subtype
β1
β2
α1
Propranolol
Carvedilol
Metoprolol
Bisoprolol
Atenolol
Nebivolol
Propanolol
Metoprolol
B. 30 times greater selectivity
Therapeutic plasma level
Receptor blockade (%)
100
80
60
40
20
0
30-fold selectivity β1 > β2
β1
β2
1
10
100
1000
10 000
100 000
Concentration
50–90% β1-blockade (desirable)
3–25% β2-blockade (undesirable)
Example: receptor blockade with 30 times greater selective β1-blocker
C. Indications and unwanted effects of the β-blockers
Therapeutic use
Migraine (prophylaxis)
Glaucoma
Hyperthyroidism
Chronic heart failure
CHD
Tachy-arrhythmias
Force ↓
Rate ↓
β1
Essential hypertension
Renin ↓
Sympathetic activity ↓
β1
Tremor
Unwanted effects
Headache
Depression
β2
Bronchoconstriction
β1
Bradycardia
AV block
Hypotension
β2
Hypoglycemia
Impotence

Fig. 12.8

Parasympathetic Nervous System

► **Responses to activation of the parasympathetic system.** Parasympathetic nerves regulate processes connected with energy assimilation (food intake, digestion, absorption) and storage. These processes operate when the body is at rest, allowing a decreased tidal volume (increased bronchomotor tone) and decreased cardiac activity. Secretion of saliva and intestinal fluids promotes the digestion of food; transport of intestinal contents is speeded up because of enhanced peristaltic activity and lowered tone of the sphincter muscles. To empty the urinary bladder (micturition), wall tension is increased by detrusor activation with a concurrent relaxation of sphincter tone.

Activation of ocular parasympathetic fibers (see below) results in narrowing of the pupil and increased curvature of the lens, enabling near objects to be brought into focus (accommodation).

► **Anatomy of the parasympathetic system.** The cell bodies of parasympathetic preganglionic neurons are located in the brainstem and the sacral spinal cord. Parasympathetic outflow is channeled from the brainstem

- through the third cranial nerve (oculomotor n.) via the ciliary ganglion to the eye;
- through the seventh cranial nerve (facial n.) via the pterygopalatine and submaxillary ganglia to lachrymal glands and salivary glands (sublingual, submandibular), respectively;
- through the ninth cranial nerve (glossopharyngeal n.) via the otic ganglion to the parotid gland; and
- via the tenth cranial nerve (vagus n.) to intramural ganglia in thoracic and abdominal viscera.

Approximately 75% of all parasympathetic fibers are contained within the vagus nerve. The neurons of the sacral division innervate the distal colon, rectum, bladder, the distal ureters, and the external genitalia.

► **Acetylcholine (ACh) as a transmitter.** ACh serves as mediator at terminals of all postganglionic parasympathetic fibers, in addition to fulfilling its transmitter role at ganglionic synapses within both the sympathetic and parasympathetic divisions and the motor end plates on striated muscle (p. 190). However, different types of receptors are present at these synaptic junctions (see table). The existence of distinct cholinoceptors at different cholinergic synapses allows selective pharmacological interventions.

Muscarinic acetylcholine receptors can be divided into five subtypes (M_1–M_5), though so far it has not been possible to influence these selectively by pharmacological means.

Table 13.1 Acetylcholine receptors

Localization of receptors	Agonist	Antagonist	Receptor type
Target tissues of 2nd parasympathetic neurons; e.g., smooth muscle, glands	ACh Muscarine	Atropine	Muscarinic (M) ACh receptor, a G-protein-coupled receptor
Sympathetic & parasympathetic gangliocytes	ACh Nicotine	Trimethaphan	Ganglionic type Nicotinic (N) ACh receptor, a ligand-gated cation channel Muscle type
Motor end plate in skeletal muscle	ACh Nicotine	*d*-Tubocurarine	

A. Responses to parasympathetic activation

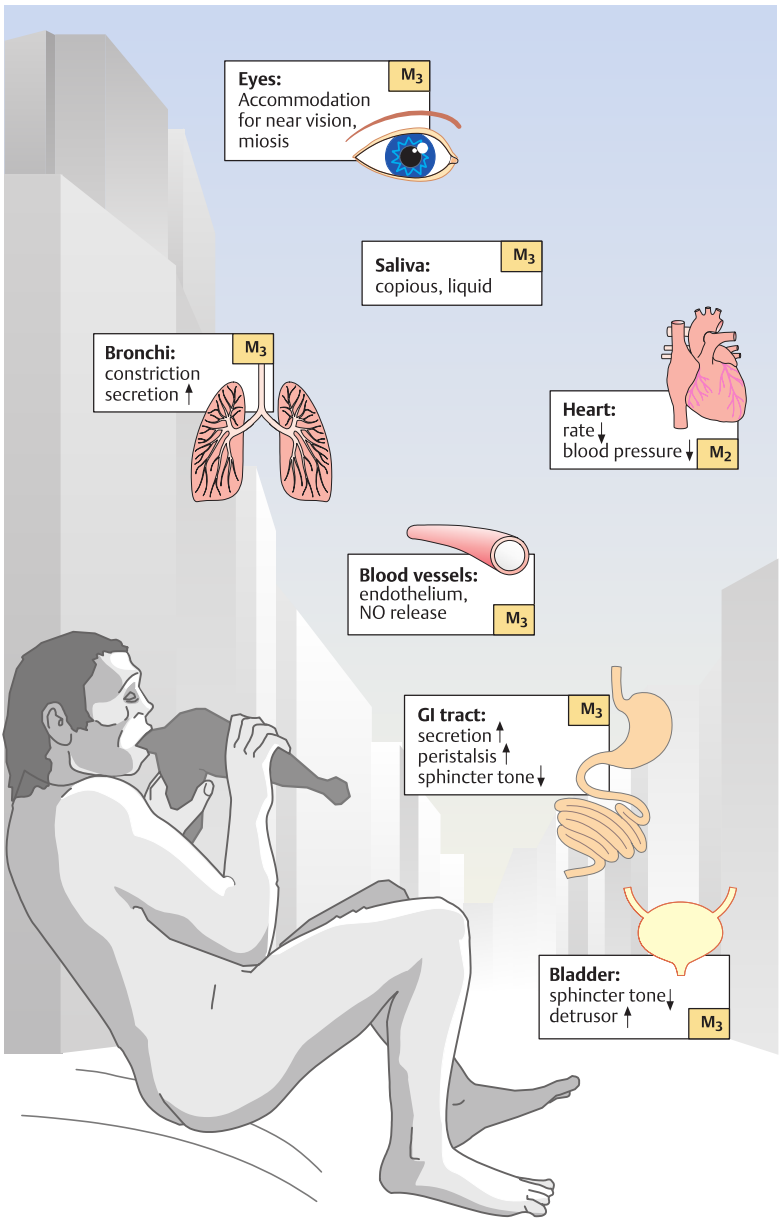


Fig. 13.1

Cholinergic Synapse

Acetylcholine (**ACh**) is the transmitter at postganglionic synapses of parasympathetic nerve endings. It is highly concentrated in synaptic storage vesicles densely present in the axoplasm of the presynaptic terminal. ACh is formed from **choline** and activated acetate (**acetyl coenzyme A**), a reaction catalyzed by the cytosolic enzyme **choline acetyltransferase**. The highly polar choline is taken up into the axoplasm by the specific choline–transporter (CHT) localized to membranes of cholinergic axon terminals and a subset of storage vesicles. During persistent or intensive stimulation, the CHT ensures that ACh synthesis and release are sustained. The newly formed ACh is loaded into storage vesicles by the vesicular ACh transporter (VAChT). The mechanism of transmitter release has been uncovered in great detail. The vesicles are anchored via the protein synapsin to the cytoskeletal network. This arrangement permits clustering of vesicles near the presynaptic membrane while preventing fusion with it. During activation of the nerve membrane, Ca^{2+} enters the axoplasm through voltage-gated channels and activates protein kinases that phosphorylate synapsin and other vesicle proteins. As a result, vesicles close to the membrane are detached from their anchoring and allowed to fuse with the presynaptic membrane. During fusion, vesicles discharge their contents into the synaptic gap and simultaneously insert CHT into the plasma membrane. ACh quickly diffuses through the synaptic gap (the acetylcholine molecule is a little longer than 0.5 nm; the synaptic gap as narrow as 20–30 nm). At the postsynaptic effector cell membrane, ACh reacts with its **receptors**. As these receptors can also be activated by the alkaloid muscarine, they are referred to as **muscarinic** (**M-**) **ACh receptors**. In contrast, at ganglionic and motor end plate (p.190) ACh receptors, the action of ACh is mimicked by nicotine and, hence, mediated by **nicotinic ACh receptors**.

Released ACh is rapidly hydrolyzed and inactivated by a specific **acetylcholinesterase**, localized to the basal lamina of motor end plates and other postsynaptic membranes. It is also cleaved by a less specific serum cholinesterase (butyrylcholinesterase), a soluble enzyme present in serum and interstitial fluid.

M-ACh receptors can be divided into five subtypes according to their molecular structure, signal transduction, and ligand affinity. Here, the M_1, M_2, and M_3 receptor subtypes are considered. M_1 receptors are present on nerve cells, especially in the brain. M_2 receptors mediate acetylcholine effects on the heart: opening of K^+ channels leads to slowing of diastolic depolarization in sinoatrial pacemaker cells and a decrease in heart rate. M_3 receptors play a role in the regulation of smooth muscle tone, e.g., in the gut and bronchi, where their activation causes stimulation of phospholipase C, membrane depolarization, and increase in muscle tone. M_3 receptors are also found in glandular epithelia, which similarly respond with activation of phospholipase C and increased secretory activity. In the CNS, where all subtypes are present, ACh receptors serve diverse functions ranging from regulation of cortical excitability, memory and learning, pain processing, and brainstem motor control.

In blood vessels, the relaxant action of ACh on muscle tone is indirect, because it involves stimulation of M_3-cholinoceptors on endothelial cells that respond by liberating NO (nitrous oxide = endothelium-derived relaxing factor). The latter diffuses into the subjacent smooth musculature, where it causes a relaxation of active tone (p. 138).

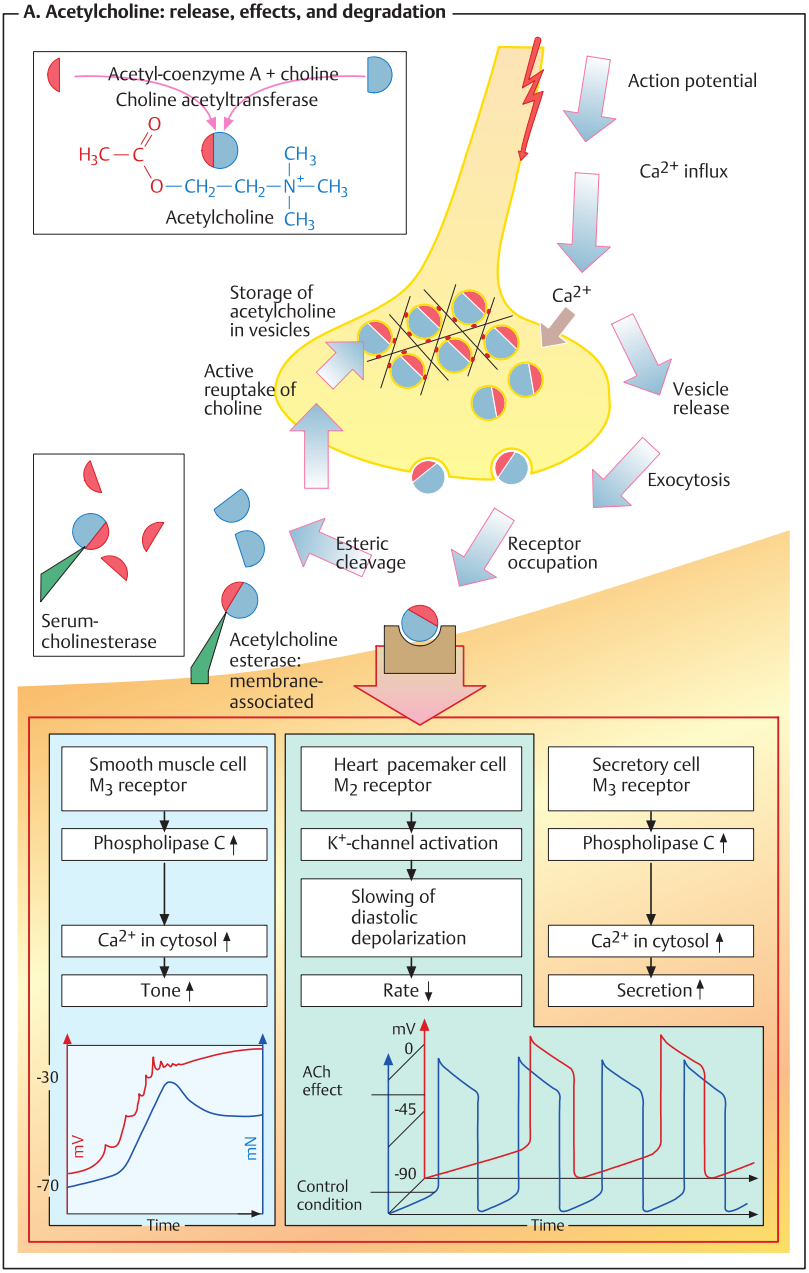

A. Acetylcholine: release, effects, and degradation
Acetyl-coenzyme A + choline
Choline acetyltransferase
Acetylcholine
Action potential
Ca2+ influx
Ca2+
Storage of acetylcholine in vesicles
Active reuptake of choline
Vesicle release
Exocytosis
Esteric cleavage
Receptor occupation
Serum-cholinesterase
Acetylcholine esterase: membrane-associated
Smooth muscle cell M3 receptor
Phospholipase C
Ca2+ in cytosol
Tone
Heart pacemaker cell M2 receptor
K+-channel activation
Slowing of diastolic depolarization
Rate
Secretory cell M3 receptor
Phospholipase C
Ca2+ in cytosol
Secretion
-30
-70
mV
mN
Time
ACh effect
Control condition
mV
0
-45
-90
Time

Fig. 13.2

Parasympathomimetics

Acetylcholine (ACh) is too rapidly hydrolyzed and inactivated by acetylcholinesterase (AChE) to be of any therapeutic use; however, its action can be replicated by other substances, namely, direct or indirect parasympathomimetics.

► **Direct parasympathomimetics.** The choline ester of carbamic acid, *carbachol,* activates M-cholinoceptors, but is not hydrolyzed by AChE. Carbachol can thus be effectively employed for local application to the eye (glaucoma). It is no longer used systemically because of its lack of organ specificity. The alkaloids *pilocarpine* (from *Pilocarpus jaborandi)* and *arecoline* (from *Areca catechu;* betel nut) also act as direct parasympathomimetics. As tertiary amines, they moreover exert central effects. The central effect of muscarine-like substances consists in an enlivening, mild stimulation that is probably the effect desired in betel chewing, a widespread habit in South Asia. Of this group, only pilocarpine enjoys therapeutic use, which is almost exclusively by local application to the eye in glaucoma (p. 346).

► **Indirect parasympathomimetics.** Indirect parasympathomimetics inhibit local AChE and raise the concentration of ACh at receptors of cholinergic synapses. This action is evident at all synapses where ACh is the mediator. Chemically, these agents include esters of carbamic acid (**carbamates** such as *physostigmine, neostigmine)* and of phosphoric acid (**organophosphates** such as *paraoxon* = E600, and *nitrostigmine* = parathion = E605, its prodrug).

Members of both groups react like ACh with AChE. The esters are hydrolyzed upon formation of a complex with the enzyme. The rate-limiting step in ACh hydrolysis is deacetylation of the enzyme, which takes only milliseconds, thus permitting a high turnover rate and activity of AChE. **Decarboxylation** following hydrolysis of a carbamate takes hours to days, the enzyme remaining inhibited as long as it is carboxylated. Cleavage of the phosphate residue, i.e., **dephosphorylation**, is practically impossible; enzyme inhibition is irreversible.

► **Uses.** The quaternary carbamate neostigmine is used to overcome the relative ACh deficiency at the motor end plate in myasthenia gravis or to reverse the neuromuscular blockade (p. 194) caused by nondepolarizing muscle relaxants (decurarization before discontinuation of anesthesia). Pyridostigmine has a similar use. The tertiary carbamate physostigmine can be used as an *antidote in poisoning with parasympatholytic drugs,* because it has access to AChE in the brain. Carbamates and organophosphates also serve as insecticides. Although they possess high acute toxicity in humans, they are more rapidly degraded than is DDT following their release into the environment.

In the early stages of **Alzheimer disease**, administration of centrally acting AChE inhibitors can bring about transient improvement in cognitive function or slow down deterioration in some patients. Suitable drugs include **rivastigmine**, **donepezil**, and **galantamine**, which require slowly increasing dosage. Peripheral side effects (inhibition of ACh breakdown) limit therapy. Donepezil and galantamine are not esters of carbamic acid and act by a different molecular action. Galantamine is also thought to promote the action of ACh at nicotinic cholinoceptors by an allosteric mechanism.

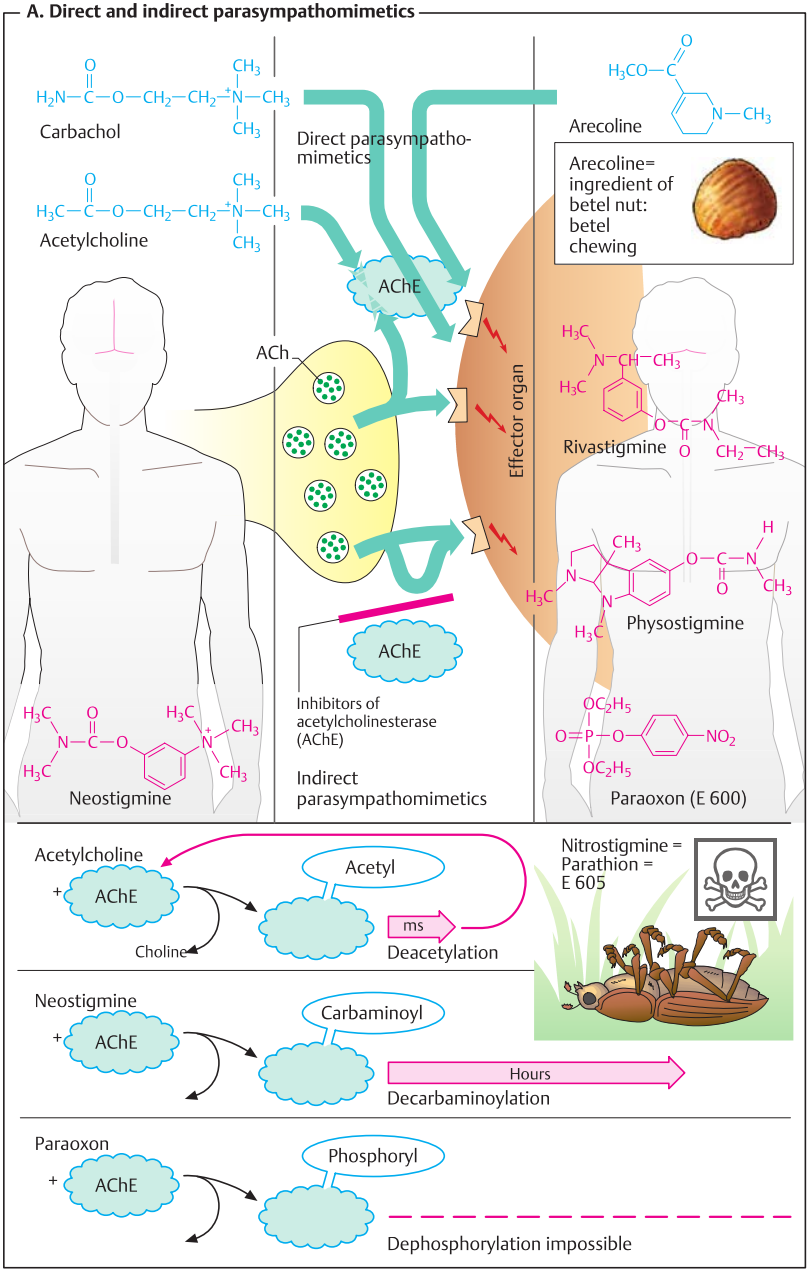

A. Direct and indirect parasympathomimetics
Carbachol
Acetylcholine
Direct parasympatho-mimetics
AChE
ACh
Effector organ
Arecoline
Arecoline= ingredient of betel nut: betel chewing
Rivastigmine
Physostigmine
Paraoxon (E 600)
Neostigmine
AChE
Inhibitors of acetylcholinesterase (AChE)
Indirect parasympathomimetics
Acetylcholine
AChE
Choline
Acetyl
ms
Deacetylation
Nitrostigmine = Parathion = E 605
Neostigmine
AChE
Carbaminoyl
Hours
Decarbaminoylation
Paraoxon
AChE
Phosphoryl
Dephosphorylation impossible

Fig. 13.3

Parasympatholytics

Excitation of the **parasympathetic** division causes release of acetylcholine at neuroeffector junctions in different target organs. The major effects are summarized in ▶ Fig. 13.4 (blue arrows). Some of these effects have therapeutic applications, as indicated by the clinical uses of parasympathomimetics (p.122).

Substances acting antagonistically at the M-cholinoceptor are designated **parasympatholytics** or **muscarinic receptor antagonists** (prototype: the alkaloid **atropine**; actions marked red in ▶ Fig. 13.4). Therapeutic use of these agents is complicated by their low organ selectivity. Possibilities for a targeted action include:

- Local application
- Selection of drugs with favorable membrane penetrability
- Administration of drugs possessing receptor subtype selectivity.

Parasympatholytics are employed for the following purposes:

▶ **1. Inhibition of glandular secretion.** *Bronchial secretion.* **Premedication** with atropine before inhalation anesthesia prevents a possible hypersecretion of bronchial mucus, which cannot be expectorated by coughing during anesthesia.

Gastric secretion. Atropine displays about equally high affinity for all muscarinic cholinoceptor subtypes and thus lacks organ specificity. Pirenzepine has preferential affinity for the M_1 subtype and was used to inhibit production of HCl in the gastric mucosa. This approach has proved inadequate because the required dosage produced too many atropine-like side effects. Also, more effective pharmacological means are available to lower HCl production, e.g., H_2-antihistamines, proton pump inhibitors (p. 184).

▶ **2. Relaxation of smooth muscle.** As a rule, administration of a parasympatholytic agent by inhalation is quite effective in **chronic obstructive pulmonary disease**. Ipratropium has a relatively short-lasting effect; four aerosol puffs usually being required per day. Tiotropium, aclidinium, and umeclidinium have high affinity for muscarinergic receptors; they bind for a particularly long time to the M_3 receptors so they need to be administered only once (tiotropium, umeclidinium) or twice (aclidinium) daily because of their "adhesiveness." They are used in COPD but are not indicated in the treatment of bronchial asthma, though they may be useful.

Spasmolysis by *N*-butylscopolamine in **biliary** or **renal colic** (p. 144). Because of its quaternary nitrogen atom, this drug does not enter the brain and requires parenteral administration. Its spasmolytic action is especially marked because of additional ganglionic blocking and direct muscle-relaxant actions.

Lowering of pupillary sphincter tone and pupillary dilation by local administration of homatropine or tropicamide (**mydriatics**) allows observation of the ocular fundus. For diagnostic use, only short-term pupillary dilation is needed. The effect of both agents subsides quickly in comparison with that of atropine (duration of several days) (see p. 346).

Muscarinic receptor antagonists with a certain selectivity for M_3 receptors can be helpful in **urge incontinence** (spasm of the detrusor muscle) and increased urgency. Detrusor muscle tone is mediated by ACh and can be reduced by *tolterodine, darifenacin, solifenacin,* and *fesoterodine.* Because of their preference for M_3 receptors, their undesirable anticholinergic effects are thought to be less than those of the nonselective antagonists. **Stress incontinence** must be distinguished; in this condition, the bladder-closing mechanism is insufficient, which becomes evident when intra-abdominal pressure is increased, for instance with sneezing or coughing. *Duloxetine* is believed to increase sphincter tone via an action in the sacral spinal cord. It is an inhibitor of norepinephrine and serotonin reuptake, and is also used as an antidepressant (p. 228).

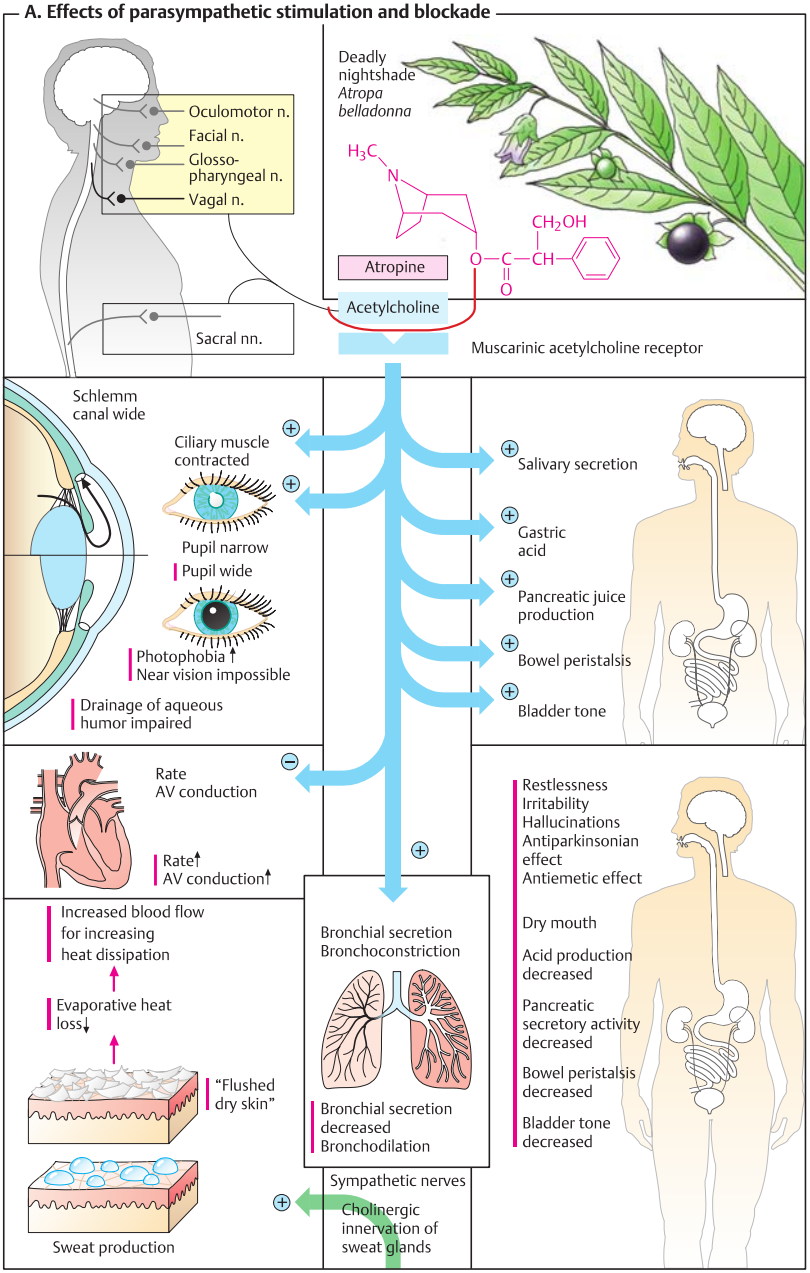

A. Effects of parasympathetic stimulation and blockade
Oculomotor n.
Facial n.
Glosso-pharyngeal n.
Vagal n.
Sacral nn.
Deadly nightshade
Atropa belladonna
Atropine
Acetylcholine
Muscarinic acetylcholine receptor
Schlemm canal wide
Ciliary muscle contracted
Pupil narrow
Pupil wide
Photophobia
Near vision impossible
Drainage of aqueous humor impaired
Salivary secretion
Gastric acid
Pancreatic juice production
Bowel peristalsis
Bladder tone
Rate
AV conduction
Rate
AV conduction
Increased blood flow for increasing heat dissipation
Evaporative heat loss
"Flushed dry skin"
Sweat production
Bronchial secretion
Bronchoconstriction
Bronchial secretion decreased
Bronchodilation
Sympathetic nerves
Cholinergic innervation of sweat glands
Restlessness
Irritability
Hallucinations
Antiparkinsonian effect
Antiemetic effect
Dry mouth
Acid production decreased
Pancreatic secretory activity decreased
Bowel peristalsis decreased
Bladder tone decreased

Fig. 13.4

► **3. Cardioacceleration.** Ipratropium is sometimes used in bradycardia and AV-block, respectively, to raise heart rate and to facilitate cardiac *impulse conduction.* As a quaternary substance, it does not penetrate into the brain, which greatly reduces the risk of CNS disturbances but not of peripheral side effects. This is why a cardiac pacemaker is preferred.

Atropine may be given to prevent **cardiac arrest** resulting from vagal reflex activation, incidental to anesthetic induction, gastric lavage, or endoscopic procedures.

► **4. CNS damping effects.** Scopolamine is effective in the *prophylaxis of kinetosis* (motion sickness, sea sickness, see p. 342); it is mostly applied by a transdermal patch. Scopolamine (pK_a = 7.2) penetrates the blood–brain barrier faster than does atropine (pK_a = 9), because at physiological pH a larger proportion is present in the neutral, membrane-permeant form.

In *psychotic excitement* (agitation), sedation can be achieved with scopolamine. Unlike atropine, scopolamine exerts a calming and amnesiogenic action that can also be used to advantage in anesthetic premedication.

Symptomatic treatment in Parkinsonism for the purpose of restoring a dopaminergic–cholinergic balance in the corpus striatum. Antiparkinsonian agents, such as biperiden (p. 334) readily penetrate the blood–brain barrier. At centrally equieffective dosages, their peripheral effects are less marked than those of atropine, though they are still considerable.

► **Contraindications for parasympatholytics.** *Closed angle glaucoma.* Since drainage of aqueous humor is impeded during relaxation of the pupillary sphincter, intraocular pressure rises.

Prostatic hyperplasia with impaired micturition: loss of parasympathetic control of the detrusor muscle exacerbates difficulties in voiding urine.

► **Atropine poisoning.** Rarely life-threatening, poisoning with atropine is characterized by the following peripheral and central effects.

Peripheral. **Tachycardia**, **dry mouth**, **hyperthermia** secondary to the inhibition of sweating. Although sweat glands are innervated by sympathetic fibers, these are cholinergic in nature. When sweat secretion is inhibited, the body loses the ability to dissipate metabolic heat by evaporation of sweat. There is a compensatory vasodilatation in the skin, allowing increased heat exchange through increased cutaneous blood flow. Decreased peristaltic activity of the intestines leads to **constipation**.

Central. Motor restlessness, progressing to maniacal agitation, psychic disturbances, **disorientation** and **hallucinations**.

Elderly subjects have an enhanced sensitivity, particularly toward the CNS toxic manifestations. In this context, the diversity of drugs producing atropine-like side effects should be borne in mind: e.g., tricyclic antidepressants, neuroleptics, antihistamines, antiarrhythmics, antiparkinsonian agents.

Apart from symptomatic, general measures (gastric lavage, cooling with ice water), **therapy of severe atropine intoxication** includes the administration of the indirect parasympathomimetic physostigmine (p.122). The most common instances of "atropine" intoxication are observed after ingestion of the berrylike fruits of belladonna (in children). A similar picture may be seen after intentional overdosage with tricyclic antidepressants in attempted suicide.

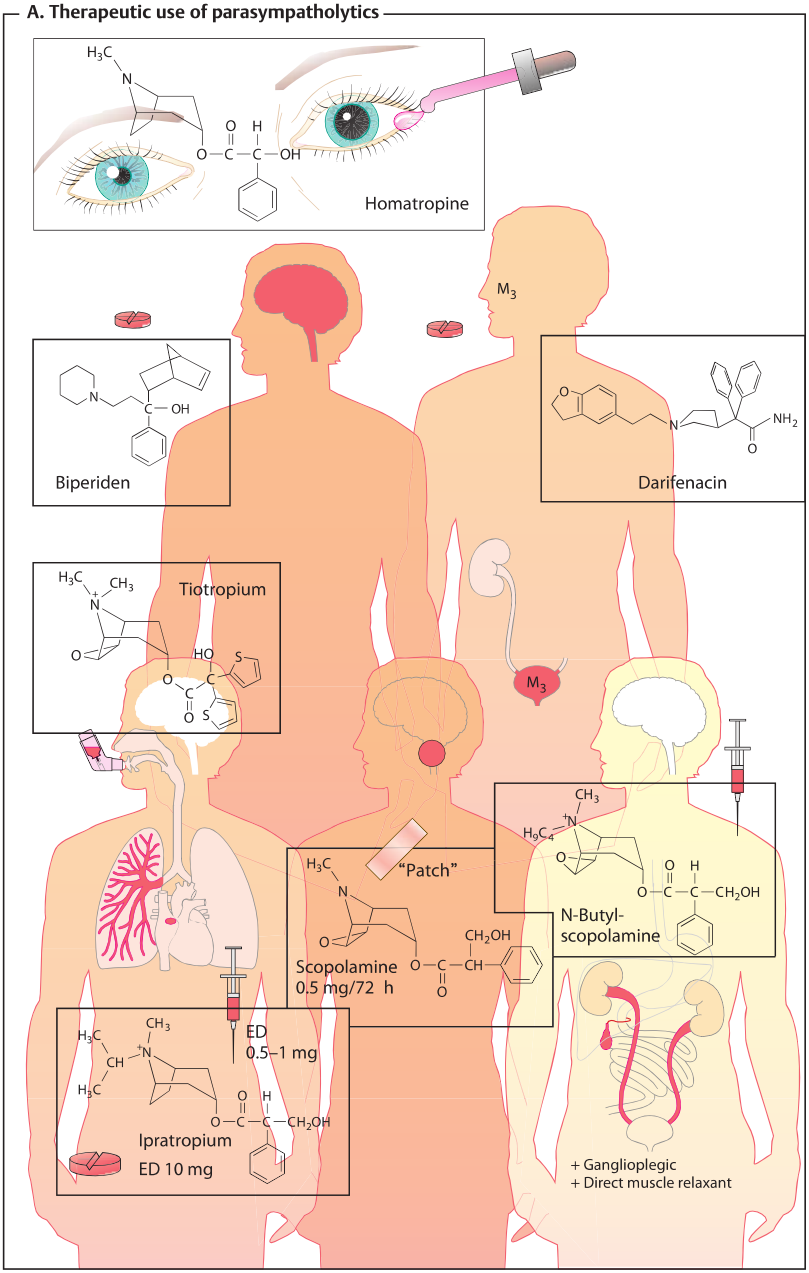

A. Therapeutic use of parasympatholytics
Homatropine
M3
Biperiden
Darifenacin
Tiotropium
M3
"Patch"
Scopolamine
0.5 mg/72 h
N-Butyl-
scopolamine
ED
0.5–1 mg
Ipratropium
ED 10 mg
+ Ganglioplegic
+ Direct muscle relaxant

Fig. 13.5

Dopamine

As a *biogenic amine*, dopamine belongs to a group of substances produced in the organism by decarboxylation of amino acids. Besides dopamine and norepinephrine formed from it, this group includes many other messenger molecules such as histamine, serotonin, and γ-aminobutyric acid.

► **Dopamine actions and pharmacological implications (► Fig. 14.1A).** In the CNS, dopamine serves as a neurotransmitter. Dopamine receptors are also present in the periphery. Dopamine released from neurons can interact with various receptor subtypes, all of which are coupled to G-proteins: the family of D_1-like receptors (comprising subtypes D_1 and D_5) and the family of D_2-like receptors (comprising subtypes D_2, D_3, and D_4). The subtypes differ in their signal transduction pathways. Thus, synthesis of cAMP is stimulated by D_1-like receptors but inhibited by D_2-like receptors.

Released dopamine can be reutilized by neuronal reuptake (specific dopamine transporter, DAT) and re-storage in vesicles (nonspecific vesicular monoamine transporter, VMAT) or can be catabolized like other endogenous catecholamines by the enzymes MAO and COMT (p.104).

Various drugs are employed therapeutically to influence dopaminergic signal transmission.

► **Antiparkinsonian agents.** In Parkinson disease, nigrostriatal dopamine neurons degenerate. To compensate for the lack of dopamine, use is made of L-dopa as the dopamine precursor and of D2 receptor agonists (for further details, see p. 334).

► **Prolactin inhibitors.** Dopamine released from hypothalamic neurosecretory nerve cells inhibits the secretion of prolactin from the adenohypophysis (p. 236). Prolactin promotes production of breast milk during the lactation period; moreover, it inhibits the secretion of gonadorelin. D_2 receptor agonists prevent prolactin secretion and can be used for weaning and the treatment of female infertility resulting from hyperprolactinemia.

The D_2 agonists differ in their duration of action and, hence, their dosing interval; e.g., bromocriptine 3 times daily, quinagolide once daily, and cabergoline once to twice weekly.

► **Antiemetics.** Stimulation of dopamine receptors in the area postrema can elicit vomiting. The area postrema is located in the floor of the 4th ventricle; its capillaries do not form part of the blood–brain barrier. D2 receptor antagonists such as metoclopramide and domperidone are used as antiemetics (p. 342). In addition, they promote gastric emptying.

► **Neuroleptics.** Various CNS-permeant drugs that exert a therapeutic action in schizophrenia display antagonist properties at D2 receptors; e.g., the phenothiazines and butyrophenone neuroleptics (p. 232).

► **Dopamine as a therapeutic agent (► Fig. 14.1B).** When given by infusion, dopamine causes a dilation of renal and splanchnic arteries that results from stimulation of D_1 receptors. This lowers cardiac afterload and augments renal blood flow, effects that are exploited in the treatment of cardiogenic shock. At progressively higher doses, dopamine is capable of activating β_1-adrenoceptors and finally α_1-receptors. In particular, α-mediated vasoconstriction would be therapeutically undesirable (symbolized by red warning sign).

Apomorphine is a dopamine agonist with a variegated pattern of usage. Given parenterally as an emetic agent to aid elimination of orally ingested poisons, it is not without hazards (hypotension, respiratory depression). In akinetic motor disturbances, it is a back-up drug. Taken orally, it was available for a time for the management of erectile dysfunction.

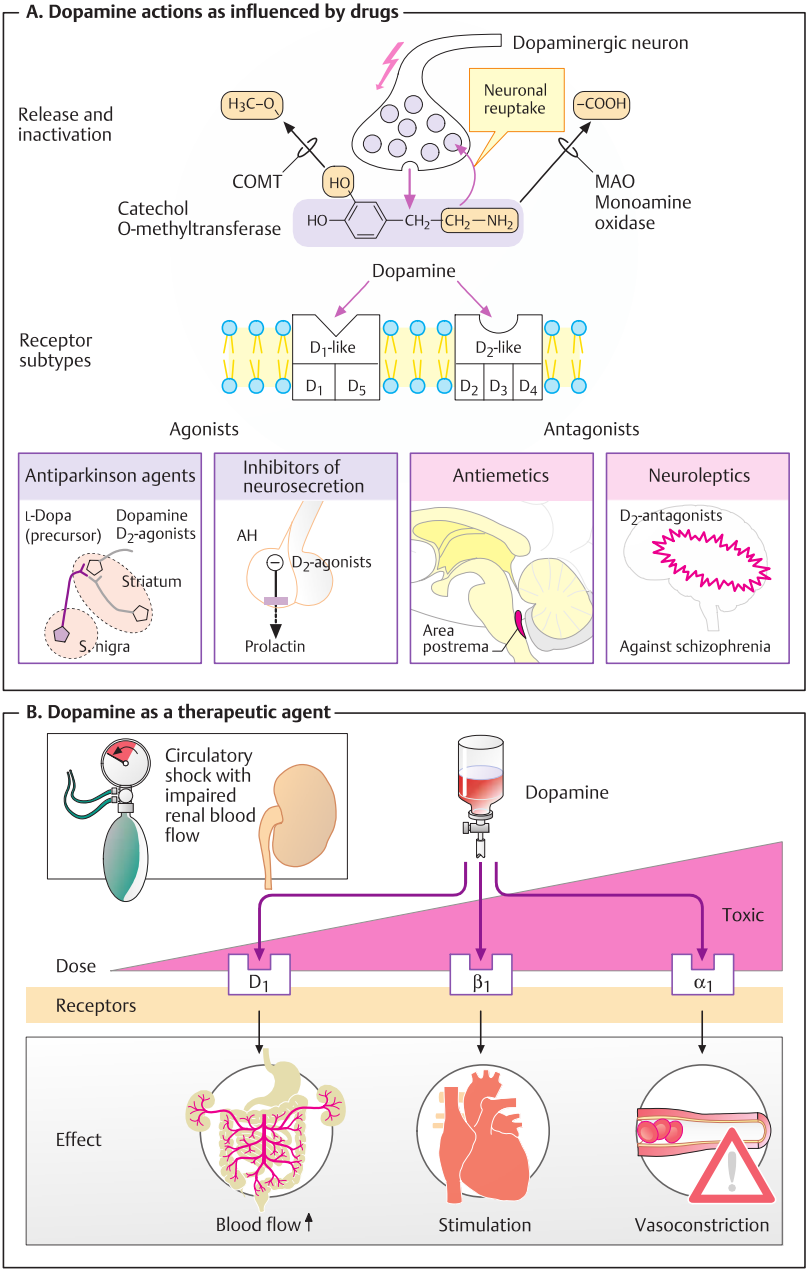

A. Dopamine actions as influenced by drugs
Dopaminergic neuron
Release and inactivation
Neuronal reuptake
H3C–O
–COOH
COMT
HO
MAO
Monoamine oxidase
Catechol O-methyltransferase
HO
CH2
CH2—NH2
Dopamine
Receptor subtypes
D1-like
D2-like
D1
D5
D2
D3
D4
Agonists
Antagonists
Antiparkinson agents
L-Dopa (precursor)
Dopamine D2-agonists
Striatum
S. nigra
Inhibitors of neurosecretion
AH
D2-agonists
Prolactin
Antiemetics
Area postrema
Neuroleptics
D2-antagonists
Against schizophrenia
B. Dopamine as a therapeutic agent
Circulatory shock with impaired renal blood flow
Dopamine
Toxic
Dose
D1
β1
α1
Receptors
Effect
Blood flow
Stimulation
Vasoconstriction

Fig. 14.1

Histamine

Histamine Effects and Their Pharmacological Properties

► **Functions.** In the CNS histamine serves as a neurotransmitter/modulator, promoting *inter alia* wakefulness. In the gastric mucosa, it acts as a mediator substance that is released from enterochromaffin-like (ECL) cells to stimulate gastric acid secretion in neighboring parietal cells (p. 184). Histamine stored in blood basophils and tissue mast cells plays a mediator role in IgE-mediated allergic reactions (p. 90). By increasing the tone of bronchial smooth muscle, histamine may trigger an asthma attack. In the intestines, it promotes peristalsis, which is evidenced in food allergies by the occurrence of diarrhea. In blood vessels, histamine increases permeability by inducing the formation of gaps between endothelial cells of postcapillary venules, allowing passage of fluid into the surrounding, tissue (e.g., wheal formation). Blood vessels are dilated because histamine induces release of nitric oxide from the endothelium (p. 138) and because of a direct vasorelaxant action. By stimulating sensory nerve endings in the skin, histamine can evoke itching.

► **Receptors.** Histamine receptors are coupled to G-proteins. The H_1 and H_2 receptors are targets for substances with antagonistic actions. The H_3 receptor is localized on nerve cells and may inhibit release of various transmitter substances, including histamine itself. A further subtype, the H_4 receptor, was discovered subsequently; this is located on certain inflammatory cells.

► **Metabolism.** Histamine-storing cells form histamine by decarboxylation of the amino acid histidine. Released histamine is degraded; no reuptake system exists as for norepinephrine, dopamine, and serotonin.

It should be mentioned that histamine can be used therapeutically in acute myeloid leukemia; it is given parenterally together with interleukin 2.

► **Antagonists.** The H_1 and H_2 receptors can be blocked by selective antagonists.

► **H1 antihistamines.** Older substances in this group (first generation) are rather nonspecific and also block other receptors (e.g., muscarinic cholinoceptors). These agents are used for the symptomatic relief of allergies (e.g., bamipine, clemastine, dimetindene, mebhydroline, pheniramine); as antiemetics (p. 342), e.g., meclizine, dimenhydrinate; and as prescription-free sedatives/hypnotics (see p. 344). Promethazine represents the transition to psychopharmaceuticals of the type of neuroleptic phenothiazines (p. 232).

Unwanted effects of most H_1 antihistamines are lassitude (impaired driving skills) and atropine-like reactions (e.g., dry mouth, constipation). Newer substances (second-generation H_1 antihistamines) do not penetrate into the CNS and are therefore practically devoid of sedative effects. Presumably they are transported back into the blood by a P-glycoprotein located in the endothelium of the blood–brain barrier. Furthermore, they hardly have any anticholinergic activity. Members of this group are: cetirizine (a racemate) and its active enantiomer levocetirizine; loratadine and its active metabolite desloratadine; terfenadine and its active metabolite fexofenadine. Bilastine, ebastine, mizolastine, and rupatadine are other new agents.

► **H_2-blockers.** H_2-blockers (p. 184) (cimetidine, ranitidine, famotidine, nizatidine) inhibit gastric acid secretion, and thus are useful in the treatment of peptic ulcers. Cimetidine may lead to drug interactions because it inhibits hepatic cytochrome oxidases. The successor drugs (e.g., ranitidine) are of less concern in this respect.

► **Mast cell stabilizers.** Cromoglicate (cromolyn) and nedocromil decrease, by an as yet unknown mechanism, the capacity of mast cells to release histamine and other mediators during allergic reactions. Both agents are applied topically (p. 354).

A. Histamine actions as influenced by drugs

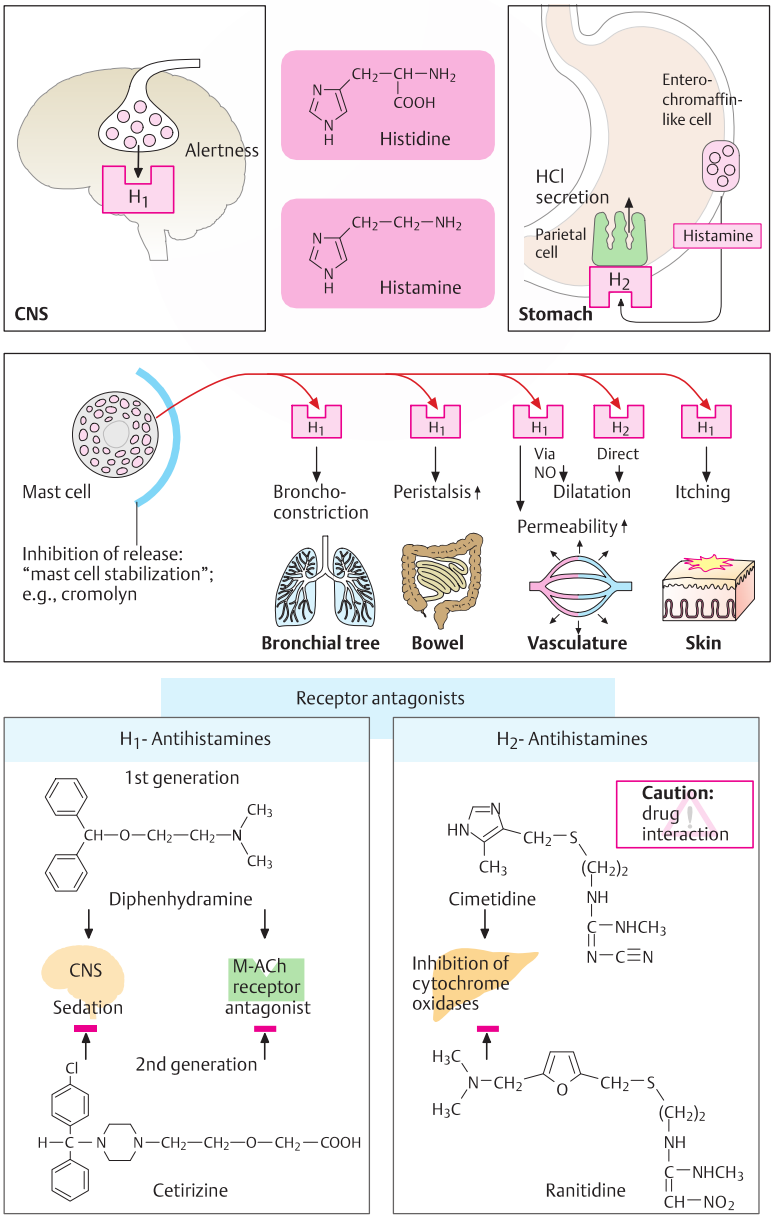


Fig. 14.2

Serotonin

Occurrence and Functions

Serotonin (5-hydroxytryptamine, 5-HT) is synthesized from L-tryptophan. Serotonin is involved as a **neurotransmitter** in a variety of functions in the **CNS**. In addition, it acts as a **messenger in the periphery**. In the intestine, it (a) acts as a neurotransmitter in the myenteric plexus and (b) is released from enterochromaffin cells (EC cells) of the intestinal epithelium to act locally as a hormone. It enhances the propulsive activity of the intestine. The EC cells can also influence the central nervous system and circulatory function indirectly. When stimulated by the presence of toxic substances in the intestine (e.g., cytostatics for cancer chemotherapy), they can induce vomiting by releasing serotonin to stimulate the afferent nerve endings of vagal nerve fibers. Moreover, they act as a "serotonin fuel station" for platelets as platelets cannot manufacture serotonin themselves. Platelet serotonin is involved in thrombus formation and blood clotting. Vascular smooth muscle can be influenced by serotonin in two opposite ways. On intact endothelial cells, it promotes the release of vasodilator messengers (NO, prostacyclin), but it has a vasoconstrictor effect by a direct action on vascular smooth muscle.

▶ **Serotonin receptors.** The body has an impressive number of different serotonin receptor subtypes. The important ones in pharmacological therapy are 5-HT_1, 5-HT_2 (both with subtypes), 5-HT_3, and 5-HT_4. Most of the receptor types are coupled to G-proteins. The 5-HT_3 subtype is a nonselective cation channel, a ligand-gated ion channel (p. 82).

▶ **Inactivation.** Like the biogenic amines norepinephrine and dopamine, serotonin released from neurons is inactivated mainly by neuronal reuptake via a specific plasmalemma serotonin transporter (SERT). Nonspecific vesicular monoamine transporter (VMAT) mediates uptake into storage vesicles. Alternatively, serotonin can be broken down within the cells by monoamine oxidases.

Promoters of Serotonin Effects

▶ **"Triptans" for migraine attacks.** *Sumatriptan* was the first agent used to treat migraine (p. 340); it acts as an agonist on 5-HT_{1D} receptors and also on 5-HT_{1B} receptors. It produces constriction of cranial vessels, possibly by inhibiting release of neuropeptides, which induce "neurogenic inflammation," or by a direct action on blood vessels. A sensation of chest tightness may occur and be indicative of coronary vasospasm. The mode of action has proven very useful and many other triptans are now on the market.

▶ **Antidepressants.** Many representatives of this group of substances inhibit neuronal reuptake of 5-HT; cf. norepinephrine–dopamine reuptake inhibitors (p. 228). Fluoxetine is the leading drug in the selective serotonin reuptake inhibitor subgroup (SSRI, ▶ Fig. 28.7).

▶ **Miscellaneous.** *Duloxetine,* which inhibits neuronal reuptake of norepinephrine and serotonin, was introduced as a treatment for stress incontinence in women and later also as an antidepressant. Prucalopride selectively stimulates the 5-HT_4 subtype, promoting gut peristalsis and acting as a laxative.

Serotonin Inhibitors

▶ **"Setrons" for cytostatic-induced emesis.** Ondansetron has an impressive protective action against vomiting following administration of cytostatic drugs. It is an antagonist at the 5-HT_3 receptor, which is located on afferent vagal nerve fibers in the intestinal mucosa and also in the brain, including the area postrema. Cytotoxic substances can be detected at both sites to initiate the process of emesis. Granisetron and the long-acting palonosetron produce analogous effects.

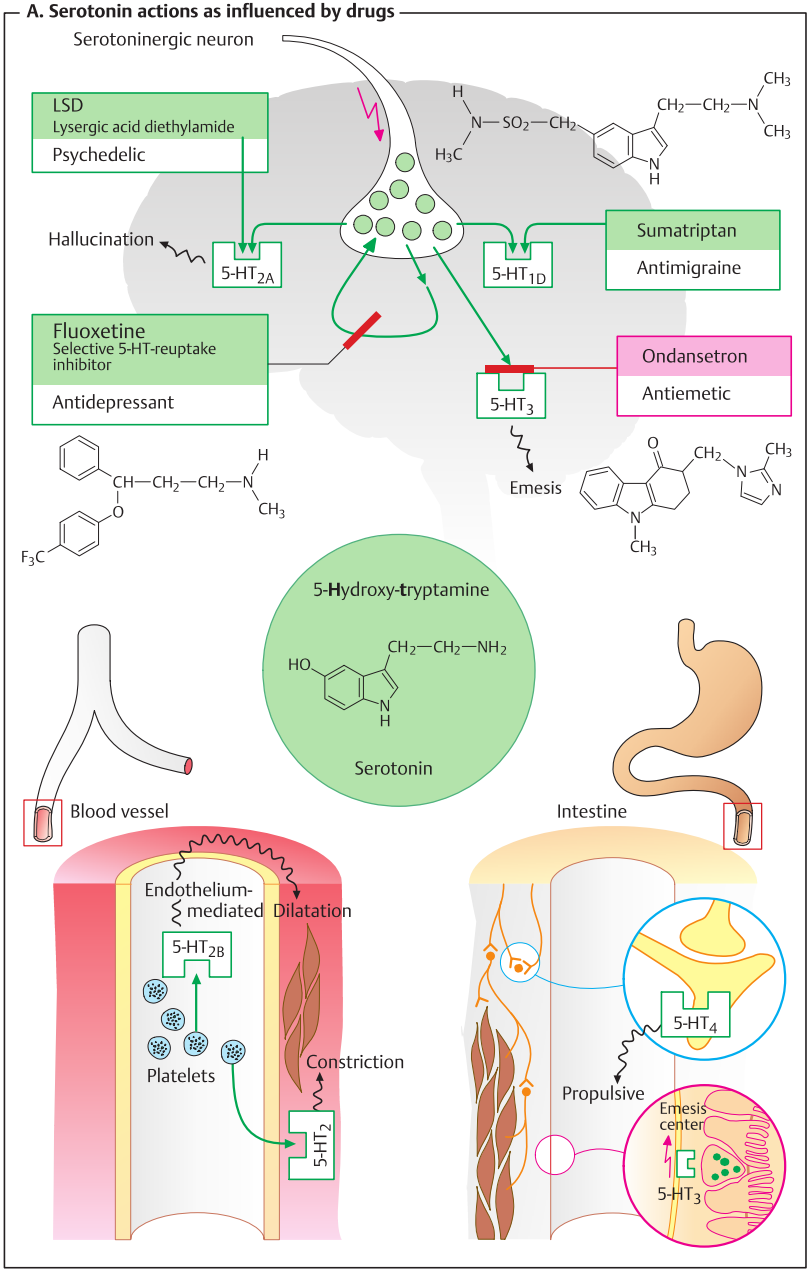

A. Serotonin actions as influenced by drugs
Serotoninergic neuron
LSD
Lysergic acid diethylamide
Psychedelic
Hallucination
5-HT2A
5-HT1D
Sumatriptan
Antimigraine
Fluoxetine
Selective 5-HT-reuptake inhibitor
Antidepressant
5-HT3
Ondansetron
Antiemetic
Emesis
5-Hydroxy-tryptamine
Serotonin
Blood vessel
Endothelium-mediated Dilatation
5-HT2B
Platelets
Constriction
5-HT2
Intestine
5-HT4
Propulsive
Emesis center
5-HT3

Fig. 14.3

Substance P

Substance P (SP) is a tachykinin and is a peptide consisting of 11 amino acids, stored in vesicles in nerve endings. When released, SP binds to special receptors called neurokinin (NK) receptors. There are three subtypes, all of which are coupled to G-proteins.

SP occurs in different sites in the body (▶ Fig. 14.4**A**):

1. Peptidergic neurons are present in the **intestinal wall**. Released SP increases intestinal muscle tone and stimulates mucosal secretion.
2. In the **visceral sensory system**. Peptidergic neurons extend from the intestinal wall to the nucleus of the tractus solitarius, and information arriving there is transmitted to various parts of the brain, such as the corpus striatum, hypothalamus, and vomiting center.
3. In **nociceptive neurons** of sensory ganglia. On stimulation, SP is released (a) as a transmitter from the axon endings in the posterior horn of the spinal cord causing an excitatory effect on the second-order neurons (anterolateral tract = pain transmission); (b) at peripheral nociceptive nerve endings, resulting in local vasodilatation or even neurogenic inflammation.

Influencing NK receptors with drugs has so far had only limited success. The NK_1 receptor, which triggers emesis by binding SP in the vomiting center, can be blocked with **aprepitant**. This antagonist action is effective in emesis caused by cytostatic agents (p. 342). Other actions of SP, such as activation of the spinothalamic tract, are not inhibited by aprepitant (no analgesic action).

Note: One feature of the somatosensory peptidergic nerve endings (not to be confused with the aforementioned viscerosensory nerves) should be mentioned briefly. They contain peripheral ion channel receptors of transient receptor potential (TRP) type. The TRPV1 (vanilloid receptor 1) subtype is activated by heat and also by constituents of pepper and paprika. This is why intensely flavored spices can elicit a sensation of heat.

Amino Acids

Two amino acids influence neuron-to-neuron impulse transmission in the CNS: (1) excitation of the postsynaptic membrane is triggered by **glutamic acid** (glutamate) and (2) impulse transmission is inhibited by γ-aminobutyric acid (GABA).

Glutamate has various receptor types at its disposal for binding (▶ Fig. 14.4**B**). Three types are ion channels. They are known as NMDA, kainate, and AMPA receptors.[1] The attachment of glutamate is very brief effect (in the millisecond range). Following release, glutamate is immediately taken up by the presynaptic neuron and especially by the closely adjacent astrocytes, which convert glutamate to glutamine, thereby inactivating it. A fourth glutamate receptor (metabotropic receptor) is coupled to G-proteins; when it is occupied, the intracellular inositol triphosphate concentration increases (long-lasting action).

γ-Aminobutyric acid (GABA) inhibits neuronal impulse transmission (▶ Fig. 14.4**C**). Two GABA receptor types can be distinguished: the $GABA_A$ receptor, with an ion pore for chloride, and the $GABA_B$ receptor, which is coupled to G-protein and inhibits cAMP production, increases K^+ conduction (hyperpolarization), and reduces Ca^{2+} permeability. Released GABA is removed rapidly from the synaptic cleft by reuptake. In the spinal cord, GABA uptake is partially replaced by the amino acid glycine. The action of tetanus toxin and the convulsant action of strychnine are due to disturbance of this system. The $GABA_A$ receptor is important for drug therapy as benzodiazepines (p. 222) specifically influence this receptor, thus acting as allosteric reinforcers of GABA action.

The $GABA_B$ receptor is stimulated by baclofen, a muscle relaxant (p. 190).

[1] NMDA = *N*-methyl-D-aspartate, kainic acid = a cyclic glutamic acid analogue, AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid.

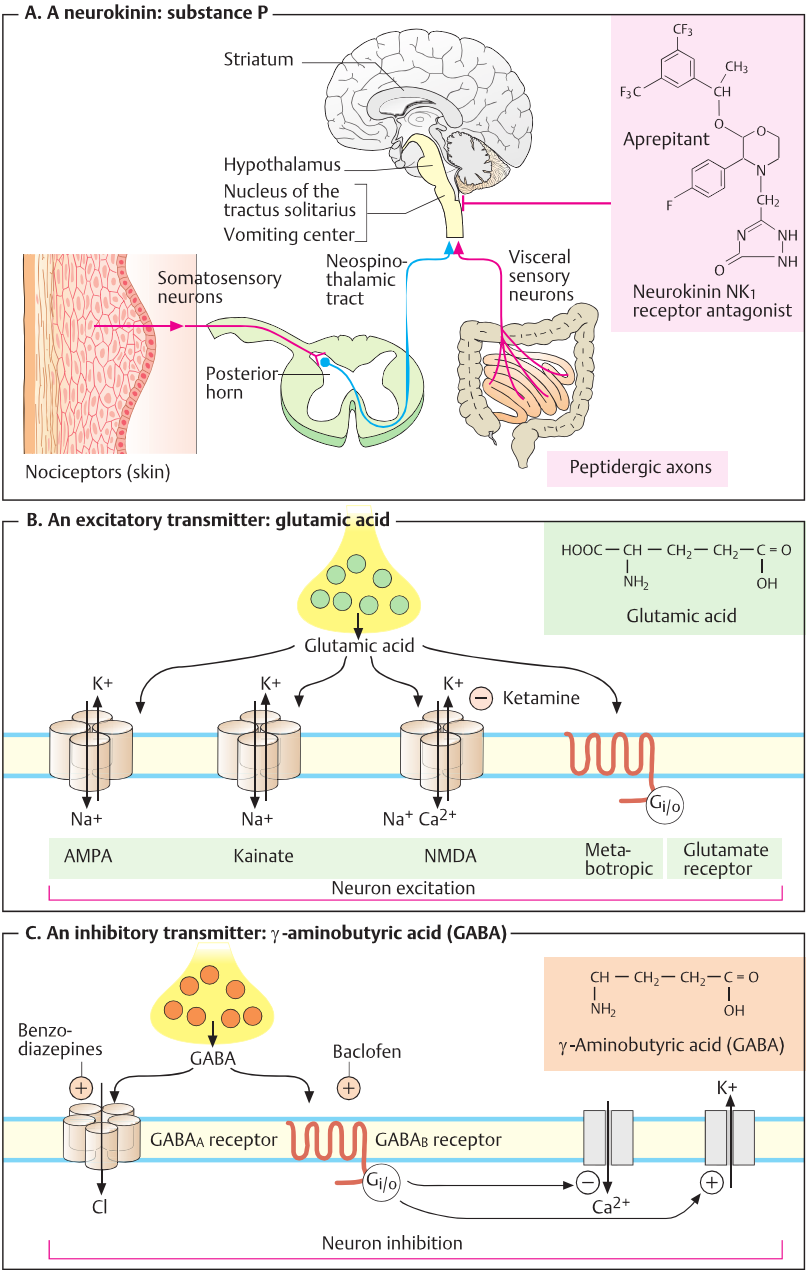

A. A neurokinin: substance P
Striatum
Hypothalamus
Nucleus of the tractus solitarius
Vomiting center
Somatosensory neurons
Neospino-thalamic tract
Visceral sensory neurons
Posterior horn
Nociceptors (skin)
Peptidergic axons
Aprepitant
Neurokinin NK1 receptor antagonist
B. An excitatory transmitter: glutamic acid
Glutamic acid
Glutamic acid
K+
Na+
Ketamine
Gi/o
AMPA
Kainate
NMDA
Meta-botropic
Glutamate receptor
Neuron excitation
C. An inhibitory transmitter: γ-aminobutyric acid (GABA)
γ-Aminobutyric acid (GABA)
Benzo-diazepines
GABA
Baclofen
GABAA receptor
GABAB receptor
Cl
Ca2+
Neuron inhibition

Fig. 14.4

Vasodilators—Overview

The distribution of blood within the circulation is a function of vascular caliber. Venous tone regulates the volume of blood returned to the heart and, hence, stroke volume and cardiac output. The luminal diameter of the arterial vasculature determines peripheral resistance. Cardiac output and peripheral resistance are prime determinants of arterial blood pressure (p. 322).

The clinically most important vasodilators are presented in ▶ Fig. 15.1**A**. Some of these agents possess different efficacy in affecting the venous and arterial limbs of the circulation.

▶ **Possible uses.** *Arteriolar vasodilators* are given to lower blood pressure in hypertension (p. 322), to reduce cardiac work in angina pectoris (p. 324), and to reduce ventricular afterload (pressure load) in cardiac failure (p. 330). *Venous vasodilators* are used to reduce venous filling pressure (preload) in angina pectoris (p. 324) or congestive heart failure (p. 330). Practical uses are indicated for each drug group.

▶ **Counterregulation in acute hypotension due to vasodilators (▶ Fig. 15.1B).** Increased *sympathetic* drive raises heart rate (reflex tachycardia) and cardiac output and thus helps to elevate blood pressure. The patients experience palpitations. Activation of the *renin–angiotensin–aldosterone (RAA) system* serves to increase blood volume, hence cardiac output. Fluid retention leads to an increase in body weight and, possibly, edemas.

These counter-regulatory processes are susceptible to pharmacological inhibition (β-blockers, renin inhibitor, ACE inhibitors, diuretics).

▶ **Mechanisms of action.** The tone of vascular smooth muscle can be decreased by various means.

Protection against vasoconstricting mediators. Renin and ACE inhibitors and angiotensin receptor antagonists protect against angiotensin II (p. 142); α-adrenoceptor antagonists interfere with (nor-) epinephrine (p. 114). Antagonists acting on endothelin (ET) receptors can abolish its vasoconstrictor effect: *bosentan* and *macitentan* block ET_A and ET_B receptors, whereas *sitaxentan* and *ambrisentan* block ET_A receptors selectively.

Substitution of vasorelaxant mediators. Analogues of prostacyclin (from vascular endothelium), such as iloprost, or of prostaglandin E_1, such as alprostadil, stimulate the corresponding receptors; organic nitrates (p. 138) substitute for endothelial NO.

Direct action on vascular smooth muscle cells. Ca^{2+} channel blockers (p. 140) and K^+ channel openers (diazoxide, minoxidil) act at the level of channel proteins to inhibit membrane depolarization and excitation of vascular smooth muscle cells. Phosphodiesterase (PDE) inhibitors retard the degradation of intracellular cGMP, which lowers contractile tonus. Several PDE isozymes with different localization and function are known. *Cilostazol* is a PDE-3 inhibitor that is believed to increase the walking distance of patients with peripheral arterial disease.

The following sections deal with special aspects:

▶ **Erectile dysfunction.** Sildenafil, vardenafil, tadalafil, and avanafil are inhibitors of PDE-5 and are used to promote erection. During sexual arousal NO is released from nerve endings in the corpus cavernosum of the penis, which stimulates the formation of cGMP in vascular smooth muscle. PDE-5, which is important in this tissue, breaks down cGMP, thus counteracting erection. Blockers of PDE-5 "conserve" cGMP. Sildenafil is now used in the treatment of pulmonary hypertension also.

▶ **Pulmonary hypertension.** This condition involves a narrowing of the pulmonary vascular bed resulting mostly from unknown causes. The disease often is progressive, associated with right ventricular overload, and all but resistant to treatment with conventional vasodilators. Endothelin receptor antagonists, sildenafil, iloprost by inhalation, or riociguat (p. 138) may produce a marked clinical improvement.

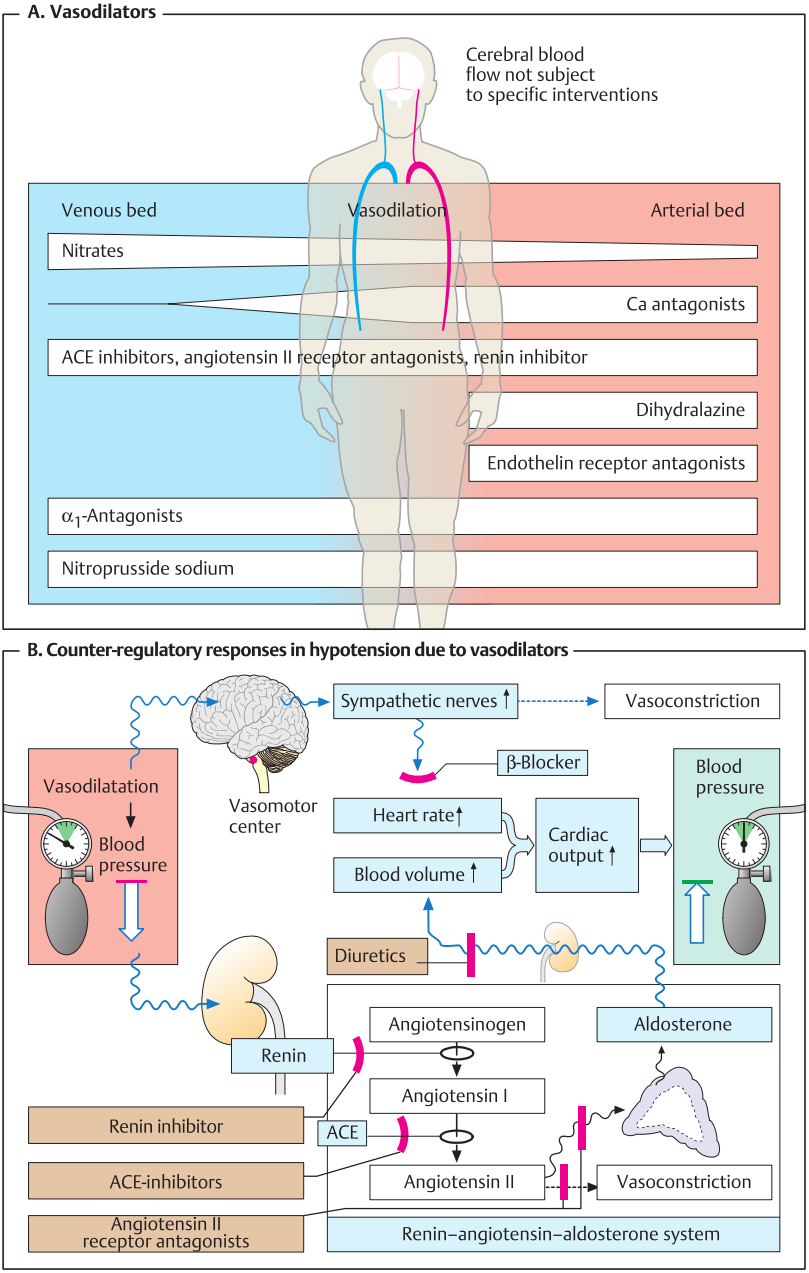

A. Vasodilators
Cerebral blood flow not subject to specific interventions
Venous bed
Vasodilation
Arterial bed
Nitrates
Ca antagonists
ACE inhibitors, angiotensin II receptor antagonists, renin inhibitor
Dihydralazine
Endothelin receptor antagonists
α1-Antagonists
Nitroprusside sodium
B. Counter-regulatory responses in hypotension due to vasodilators
Sympathetic nerves
Vasoconstriction
β-Blocker
Vasodilatation
Blood pressure
Vasomotor center
Heart rate
Blood volume
Cardiac output
Blood pressure
Diuretics
Angiotensinogen
Aldosterone
Renin
Angiotensin I
Renin inhibitor
ACE
ACE-inhibitors
Angiotensin II
Vasoconstriction
Angiotensin II receptor antagonists
Renin–angiotensin–aldosterone system

Fig. 15.1

Organic Nitrates

Various esters of nitric acid (HNO_3) and polyvalent alcohols relax vascular smooth muscle, e.g., nitroglycerin (glyceryl trinitrate) and isosorbide dinitrate. *The effect is more pronounced in venous than in arterial beds.*

These vasodilator effects produce hemodynamic consequences that can be put to therapeutic use. Owing to a decrease in both venous return (preload) and arterial afterload, cardiac work is decreased (p. 324). As a result, the cardiac oxygen balance improves. Spasmodic constriction of larger coronary vessels (coronary spasm) is prevented.

Uses. Organic nitrates are used chiefly in angina pectoris (p. 324), less frequently in severe forms of chronic and acute congestive heart failure. Continuous intake of higher doses with maintenance of steady plasma levels leads to loss of efficacy, inasmuch as the organism becomes refractory (tachyphylactic). This "nitrate tolerance" can be avoided if a daily "nitrate-free interval" is maintained, e.g., overnight.

At the start of therapy, a **reaction** occurs frequently in the form of a throbbing headache, probably caused by dilation of cephalic vessels. This effect also exhibits tolerance, even with daily "nitrate pauses." Excessive dosages give rise to hypotension, reflex tachycardia, and circulatory collapse.

► **Mechanism of action.** The reduction in vascular smooth muscle tone is due to activation of guanylate cyclase and elevation of cellular cyclic GMP levels. The causative agent is nitric oxide (NO) generated from the organic nitrate. NO is a physiological messenger molecule that endothelial cells release onto subjacent smooth muscle cells ("endothelium-derived relaxant factor," EDRF). Organic nitrates thus utilize a physiological pathway; hence their high efficacy. The enzymatically mediated generation of NO from organic nitrates (via a mitochondrial aldehyde dehydrogenase) within the smooth muscle cell depends on a supply of free sulfhydryl (-SH) groups; "nitrate-tolerance" is attributed to a cellular exhaustion of SH donors.

Glycerol trinitrate (GTN; nitroglycerin) is distinguished by a high membrane penetrability and very low stability. It is the drug of choice in the treatment of angina pectoris attacks. For this purpose, it is administered as a spray, or in sublingual or buccal tablets for transmucosal delivery. The onset of action is between 1 and 3 minutes. Due to a nearly complete presystemic elimination, it is poorly suited for oral administration. Transdermal delivery (nitroglycerin patch) also avoids presystemic elimination.

Isosorbide dinitrate (ISDN) penetrates well through membranes, is more stable than NTG, and is partly degraded into the weaker, but much longer-acting, 5-isosorbide mononitrate. ISDN can also be applied sublingually; however, it is mainly administered orally in order to achieve a prolonged effect.

Isosorbide mononitrate (ISMN) is not suitable for sublingual use because of its higher polarity and slower rate of absorption. Taken orally, it is absorbed and is not subject to first-pass elimination.

Molsidomine itself is inactive. After oral intake, it is slowly converted into an active metabolite, linsidomine. The differential effectiveness in arterial vs. venous beds is less evident compared to the drugs mentioned above. Moreover, development of "nitrate tolerance" is of less concern. These differences in activity profile appear to reflect a different mechanism of NO release. The same applies to sodium nitroprusside.

Sodium nitroprusside contains a nitroso (–NO) group, but is not an ester. It dilates venous and arterial beds equally. It is administered by infusion to achieve *controlled hypotension* under continuous close monitoring. Cyanide ions liberated from nitroprusside can be inactivated with sodium thiosulfate (p. 310).

Riociguat can promote cGMP synthesis by direct stimulation of soluble guanylate cyclase, reducing vascular smooth muscle tone in pulmonary hypertension (p. 136).

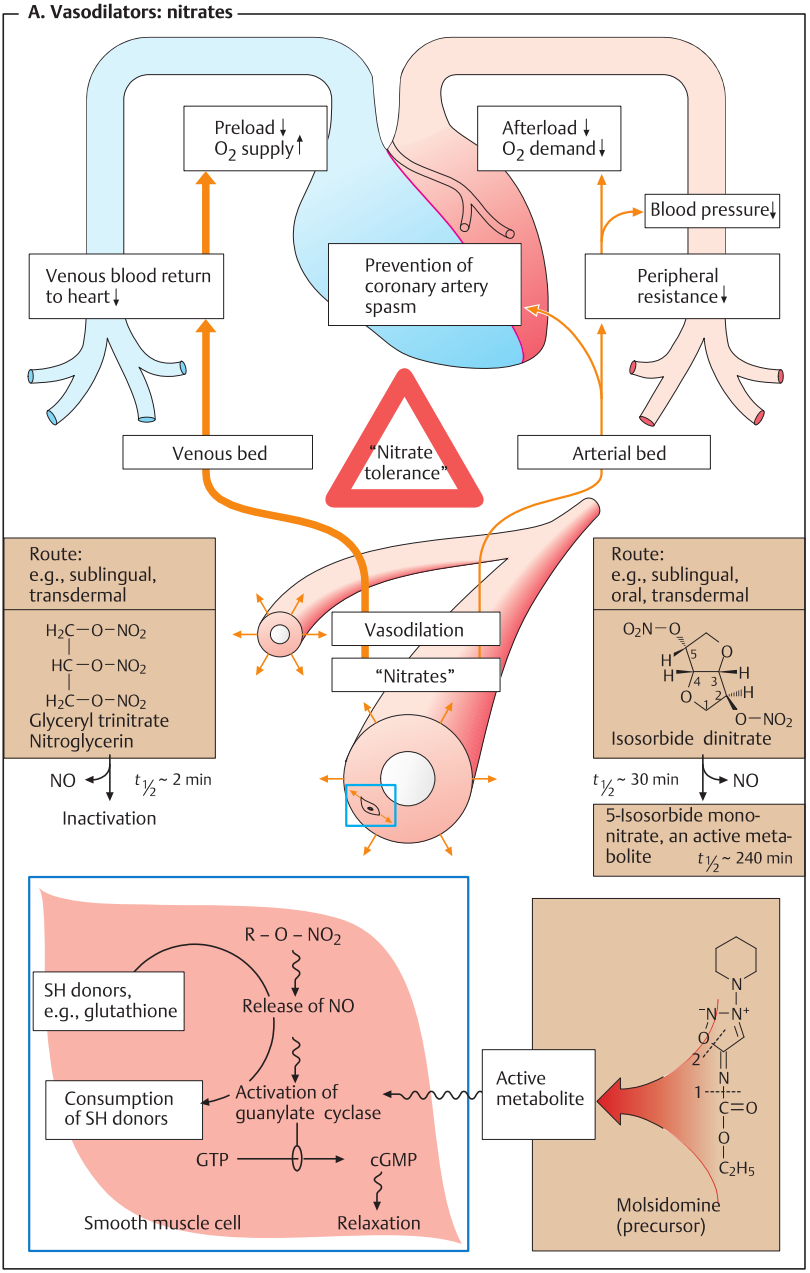

A. Vasodilators: nitrates
Preload ↓
O_2 supply ↑
Afterload ↓
O_2 demand ↓
Blood pressure ↓
Venous blood return to heart ↓
Prevention of coronary artery spasm
Peripheral resistance ↓
Venous bed
"Nitrate tolerance"
Arterial bed
Route:
e.g., sublingual, transdermal
$H_2C-O-NO_2$
$HC-O-NO_2$
$H_2C-O-NO_2$
Glyceryl trinitrate
Nitroglycerin
NO
$t_{1/2}$ ~ 2 min
Inactivation
Vasodilation
"Nitrates"
Route:
e.g., sublingual, oral, transdermal
O_2N-O
$O-NO_2$
Isosorbide dinitrate
$t_{1/2}$ ~ 30 min
NO
5-Isosorbide mononitrate, an active metabolite
$t_{1/2}$ ~ 240 min
R – O – NO_2
SH donors, e.g., glutathione
Release of NO
Consumption of SH donors
Activation of guanylate cyclase
GTP
cGMP
Smooth muscle cell
Relaxation
Active metabolite
Molsidomine (precursor)

Fig. 15.2

Calcium Antagonists

During electrical excitation of the cell membrane of heart or smooth muscle, different ionic currents are activated, including an inward Ca^{2+} current. The term Ca^{2+} antagonist is applied to drugs that inhibit the influx of Ca^{2+} ions without affecting inward Na^+ or outward K^+ currents to a significant degree. Other labels are *calcium entry blocker* or *Ca^{2+} channel blocker*. Ca^{2+} antagonists used therapeutically can be divided into two groups according to their effects on heart and vasculature.

► **I. Dihydropyridine Derivatives.** The dihydropyridines, e.g., **nifedipine**, are uncharged hydrophobic substances. They particularly induce a *relaxation* of vascular smooth muscle in *arterial beds*. An effect on cardiac function is practically absent at therapeutic dosage. They are thus regarded as *vasoselective Ca^{2+} antagonists*. Because of the dilation of resistance vessels, blood pressure falls. Cardiac afterload is diminished (p. 324) and, therefore, also oxygen demand. Spasms of coronary arteries are prevented.

► **Indications.** Slow-release forms of nifedipine can be used in chronic angina pectoris and essential hypertension. Rapidly released forms of nifedipine should be used only in hypertensive emergencies because of the reflex tachycardia they produce. **Adverse effects** are tachycardia (due to hypotension, which may increase the risk of myocardial infarction), headache, and pretibial edema.

The successor substances principally exert the same effects, but have different kinetic properties (slow elimination and, hence, steady plasma levels).

Nitrendipine, isradipine, and *felodipine* are used to treat hypertension. *Nisoldipine* is also used in angina pectoris. *Nimodipine* is given prophylactically after subarachnoid hemorrhage to prevent vasospasms. On its dihydropyridine ring, *amlodipine* possesses a side chain with a protonatable nitrogen and hence can exist in a positively charged state. This influences its pharmacokinetics, as evidenced by the very long half-life of elimination (~40 hours). The "ultra-short-acting" clevidipine is given i.v. for acute blood pressure reduction during surgery.

► **II. Verapamil and other catamphiphilic Ca^{2+} antagonists.** Verapamil contains a nitrogen atom bearing a positive charge at physiological pH and represents a *cationic amphiphilic molecule*. It exerts inhibitory effects on *arterial smooth muscle*, and also on *heart muscle*. In the heart, Ca^{2+} inward currents are important in generating depolarization of sinoatrial node cells (impulse generation), in impulse propagation through the AV junction (atrioventricular conduction), and in electromechanical coupling in ventricular cardiomyocytes. Verapamil thus produces negative chronotropic, dromotropic, and inotropic effects.

► **Indications.** Verapamil is used as an *antiarrhythmic drug* in supraventricular tachyarrhythmias. In atrial flutter or fibrillation, it is effective in reducing ventricular rate by virtue of inhibiting AV conduction. Verapamil is also employed in the prophylaxis of *angina pectoris attacks* (p. 326) and the treatment of *hypertension* (p. 322).

► **Adverse effects.** Because of verapamil's effects on the sinus node, a drop in blood pressure fails to evoke a reflex tachycardia. Heart rate hardly changes; bradycardia may even develop. AV block and myocardial insufficiency can occur. Patients frequently complain of constipation, because verapamil also inhibits intestinal musculature. In contrast to the dihydropyridines, verapamil must not be given in combination with β-blockers because of the risk of AV block.

Diltiazem is a catamphiphilic benzothiazepine derivative with an activity profile resembling that of verapamil.

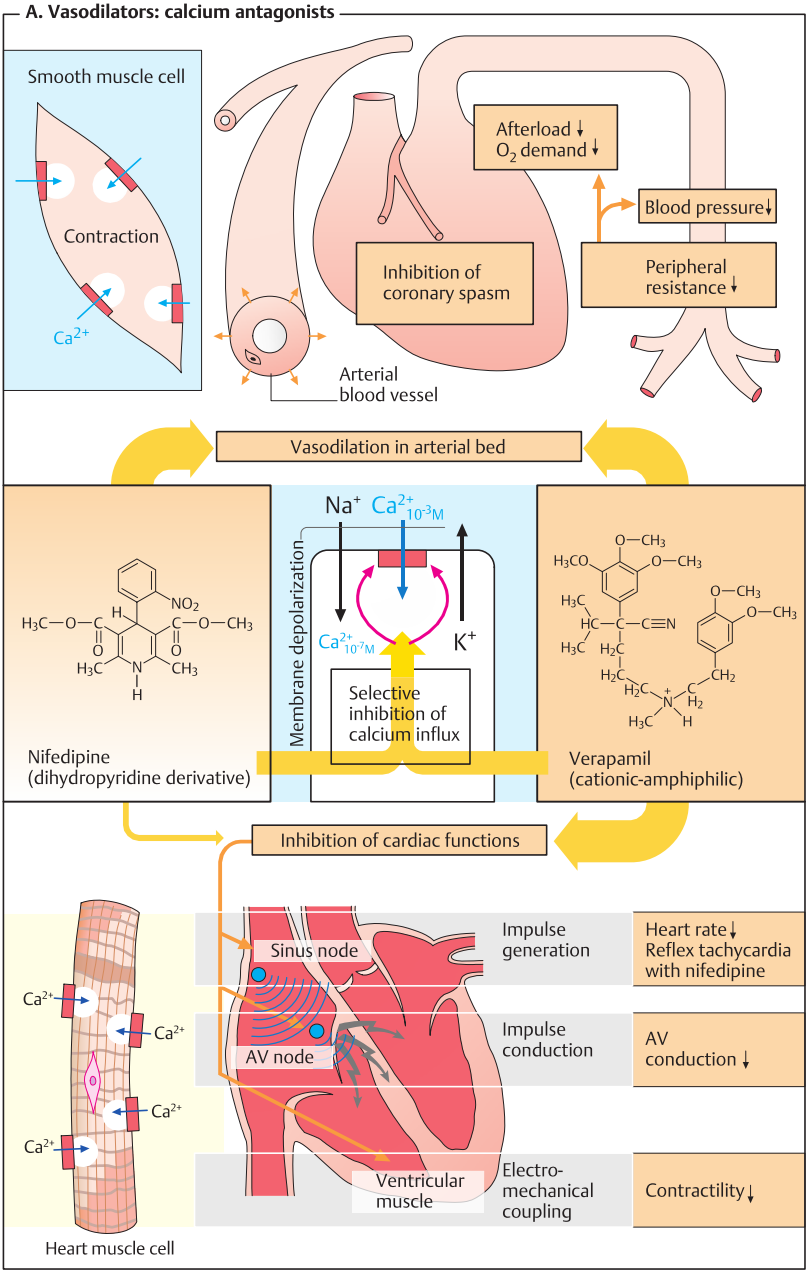

A. Vasodilators: calcium antagonists
Smooth muscle cell
Contraction
Ca2+
Afterload ↓
O2 demand ↓
Blood pressure ↓
Peripheral resistance ↓
Inhibition of coronary spasm
Arterial blood vessel
Vasodilation in arterial bed
Na+
Ca2+ 10-3M
Membrane depolarization
Ca2+ 10-7M
K+
Selective inhibition of calcium influx
Nifedipine (dihydropyridine derivative)
Verapamil (cationic-amphiphilic)
Inhibition of cardiac functions
Sinus node
AV node
Ventricular muscle
Impulse generation
Impulse conduction
Electro-mechanical coupling
Heart rate ↓ Reflex tachycardia with nifedipine
AV conduction ↓
Contractility ↓
Heart muscle cell

Fig. 15.3

Inhibitors of the Renin–Angiotensin–Aldosterone System

The renin–angiotensin–aldosterone system regulates blood pressure along with sodium and water homeostasis (▶ Fig. 16.1A).

Renin is produced by specialized smooth muscle cells in the wall of the afferent arteriole of the renal glomerulus (juxtaglomerular apparatus). Stimuli eliciting release of renin are: a drop in renal perfusion pressure and sympathetic activation of β-adrenoceptors in juxtaglomerular cells. As soon as renin is secreted into the blood, it cleaves the decapeptide angiotensin I from angiotensinogen, which is produced in the liver. The enzyme ACE, in turn, produces biologically active angiotensin II from angiotensin I.

ACE circulates in the plasma and is located on the surface of endothelial cells. It is a non-specific peptidase that can cleave C-terminal dipeptides from various peptides (dipeptidyl carboxypeptidase). In this way, ACE helps to inactivate kinins, e.g., bradykinin.

Angiotensin II can activate two different receptors, AT_1 and AT_2, both of which are coupled to G-proteins. The most important cardiovascular actions of angiotensin II are mediated through AT_1 receptors (▶ Fig. 16.1A). Angiotensin II increases blood pressure in various ways: (1) vasoconstriction in both the arterial and venous limbs of the circulation; (2) stimulation of aldosterone secretion leading to increased renal reabsorption of NaCl and water and therefore increased blood volume; (3) a central increase in sympathetic tone and, peripherally, enhanced release and effects of norepinephrine. Chronically elevated levels of angiotensin II can give rise to hypertrophy of muscle cells in the heart and arteries and an increase in connective tissue (fibrosis).

ACE inhibitors, such as **captopril** and **enalaprilate** occupy the active center of the enzyme so that cleavage of angiotensin I is inhibited competitively. Indications are hypertension and chronic cardiac failure. Lowering of the elevated blood pressure is predominantly brought about by diminished production of angiotensin II. Impaired degradation of kinins that exert vasodilating actions may contribute to the effect.

In **congestive heart failure**, cardiac output rises after administration of an ACE inhibitor because ventricular afterload diminishes owing to a fall in peripheral resistance. Venous congestion (preload) abates and there is a reduction in aldosterone secretion and in the tone of the venous capacitance vessels.

▶ **Adverse effects.** When the RAA system is activated by loss of electrolytes and water, (e.g., as a result of treatment with diuretic drugs, cardiac failure, or renal artery stenosis), administration of ACE inhibitors may initially cause an excessive fall in blood pressure. Dry cough is a fairly frequent side effect (10%), possibly caused by reduced inactivation of kinins in the bronchial mucosa. Combination of ACE inhibitors with potassium-sparing diuretics can lead to hyperkalemia. In most cases, ACE inhibitors are well tolerated and effective.

Newer analogues include lisinopril, ramipril, quinapril, fosinopril, benazepril, and zofenopril.

▶ **Antagonists at AT_1 angiotensin II receptors ("sartans").** Blocking of the AT_1 receptor by an antagonist suppresses the action of angiotensin II. **Losartan** was the first drug in the sartan group, and analogues were soon developed. These include azilsartan, candesartan, eprosartan, irbesartan, olmesartan, telmisartan, and valsartan. The main (antihypertensive) effects and side effects resemble those of ACE inhibitors. However, because they do not inhibit degradation of kinins, they do not cause dry cough.

▶ **Renin inhibitor.** A direct renin inhibitor, which can be used for the treatment of hypertension, has been available since 2007 (**aliskiren**). This drug is absorbed poorly after oral administration (bioavailability 3%) and is eliminated very slowly, with a half-life of 40 hours. Its spectrum of action is similar to that of AT_1 receptor antagonists.

▶ **Neprilysin inhibitor.** Recently, the combination of the neprilysin inhibitor sacubitril with the AT_1 receptor antagonist valsartan was approved for treatment of chronic heart failure. Neprilysin catalyzes breakdown of natriuretic peptides (ANP, BNP) and degradation of angiotensin II. Sacubitril increases levels of natriuretic peptides which stimulate vasodilatation and natriuresis and inhibit cardiac remodeling. Valsartan is added to prevent detrimental effects of increased angiotensin II.

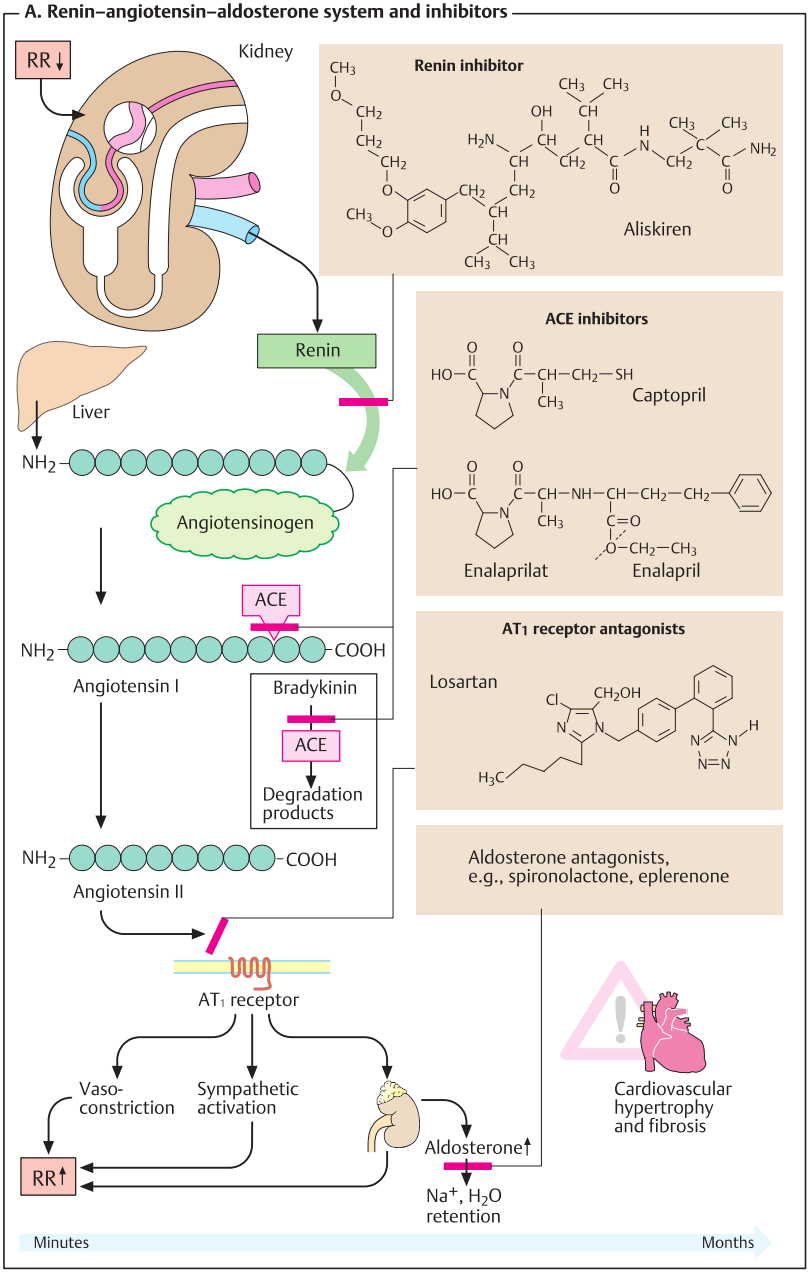

A. Renin–angiotensin–aldosterone system and inhibitors
RR↓
Kidney
Renin
Liver
NH2
Angiotensinogen
ACE
NH2
COOH
Angiotensin I
Bradykinin
ACE
Degradation products
NH2
COOH
Angiotensin II
AT1 receptor
Vaso-constriction
Sympathetic activation
RR↑
Aldosterone↑
Na+, H2O retention
Cardiovascular hypertrophy and fibrosis
Minutes
Months
Renin inhibitor
Aliskiren
ACE inhibitors
Captopril
Enalaprilat
Enalapril
AT1 receptor antagonists
Losartan
Aldosterone antagonists, e.g., spironolactone, eplerenone

Fig. 16.1

Drugs Used to Influence Smooth Muscle Organs

► **Bronchodilators.** Narrowing of bronchioles raises airway resistance, e.g., in bronchial or bronchitic asthma. Several substances that are employed as *bronchodilators* are described elsewhere in more detail: β_2-sympathomimetics (p. 110; given by pulmonary, parenteral, or oral route), the methylxanthine *theophylline* (p. 354; given parenterally or orally), and the parasympatholytics (p. 124) *ipratropium* and *tiotropium*.

► **Spasmolytics.** *N-Butylscopolamine* (p. 124) is used for the relief of painful spasms of the bile ducts or ureters. Its poor absorption (N.B.: quaternary N; absorption rate < 10%) necessitates parenteral administration. Because the therapeutic effect is usually weak, a potent analgesic is given concurrently, e.g., the opioid meperidine. Note that some spasms of intestinal musculature can be effectively relieved by organic nitrates (in biliary colic) or by nifedipine (achalasia: esophageal spasm).

► **Myometrial relaxants (tocolytics).** *β_2-Sympathomimetics* such as fenoterol, given orally or parenterally, can prevent threatened abortion or interrupt labor in progress when dangerous complications necessitate caesarean section. Tachycardia is a side effect produced reflexly because of β_2-mediated vasodilation or a direct stimulation of cardiac β_1-receptors. *Atosiban,* a structurally altered oxytocin derivative, has become available. It acts as an antagonist at oxytocin receptors, is given parenterally, and lacks the cardiovascular side effects of β_2-sympathomimetics, but often causes nausea and vomiting.

► **Myometrial stimulants.** The neurohypophyseal hormone *oxytocin* (p. 236) is given parenterally (or by the nasal or buccal route) before, during, or after labor in order to prompt uterine contractions or to enhance them. *Carbetocin* is a long-acting analogue, which is used to increase uterine tone following caesarean section. Certain *prostaglandins* or analogues of them (p. 198), e.g., dinoprostone, sulprostone, are capable of inducing rhythmic uterine contractions and cervical relaxation at any time. They are mostly employed as abortifacients (local or parenteral administration).

Ergot alkaloids are obtained from *Secale cornutum* (ergot), the sclerotium of a fungus *(Claviceps purpurea)* parasitizing rye. Consumption of flour from contaminated grain was once the cause of epidemic poisonings *(ergotism)* characterized by gangrene of the extremities (St. Anthony's fire) and CNS disturbances (hallucinations).

The ergot alkaloids are derivatives of lysergic acid (see ergotamine formula in **A**). The therapeutic importance of the native alkaloids has diminished greatly. **Ergometrine**, which has a predominantly stimulating effect on the myometrium, is no longer used to increase contractions during labor, as it induces uterine tetany too readily, acutely endangering the fetus. Methylation of this alkaloid to give methylergometrine produces a drug that can be used to stimulate the uterus to contract **after delivery**. Apart from ergometrine, ergot also contains ergotamine and various ergotoxin alkaloids. The only native ergot alkaloid in use is ergotamine, which is administered in the short term in treatment-resistant migraine attacks (p. 340).

A few semisynthetic lysergic acid derivatives have specific receptor affinities and can be used therapeutically; an example is the dopamine agonist **bromocriptine** (p. 128).

Lysergic acid diethylamide (LSD) has a particular significance as it can produce "model psychosis" in oral doses of only 0.02–0.4 mg (see p. 312).

A. Drugs used to alter smooth-muscle function

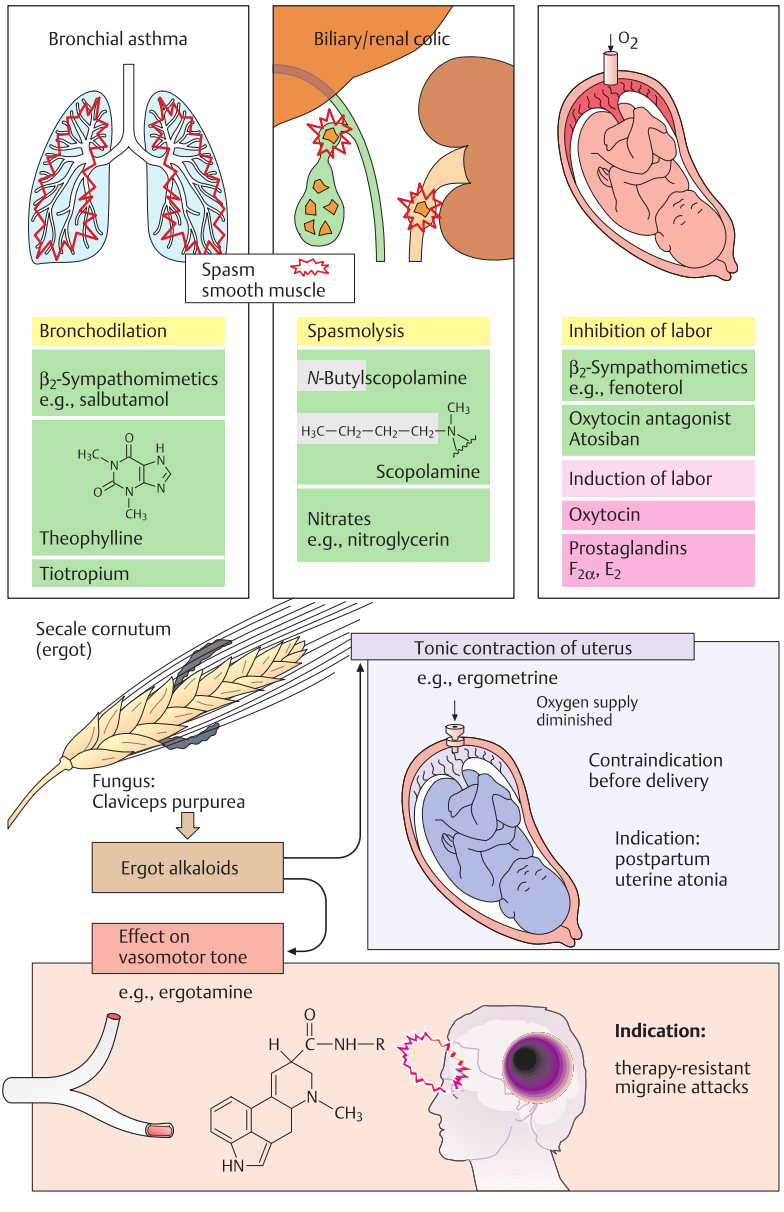


Fig. 17.1

Cardiac Drugs

► **Possible ways of influencing heart function.** The pumping capacity of the heart depends on different factors (► Fig. 18.1A): with increasing heart rate, the force of contraction increases ("positive staircase"); the degree of diastolic filling regulates contraction amplitude (Starling's law of the heart). The sympathetic innervation with its transmitter norepinephrine and the hormone epinephrine promote contractile force generation (but also oxygen consumption), and raise the heart rate and excitability (p. 106). The parasympathetic innervation lowers the rate because acetylcholine inhibits pacemaker cells (p. 120).

From the influence of the autonomic nervous system it follows that all sympatholytic or sympathomimetic and parasympatholytic or parasympathomimetic drugs can produce corresponding effects on cardiac performance. These possibilities are exploited therapeutically: for instance, β-blockers (p. 116) for suppressing excessive sympathetic drive; ipratropium for treating sinus bradycardia (p. 126). An unwanted activation of the sympathetic system can result from anxiety, pain, and other emotional stress. In these cases, the heart can be protected from harmful stimulation by psychopharmaceuticals such as benzodiazepines (diazepam and others; important in myocardial infarction).

Cardiac work furthermore depends strongly on the state of the circulation system: physical rest or work demand appropriate cardiac performance; the level of mean blood pressure is an additional decisive factor. Chronic elevation of afterload leads to myocardial insufficiency. Therefore, all blood pressure-lowering drugs can have an important therapeutic influence on the myocardium. Vasodilator substances (e.g., nitrates) lower the venous return and/or peripheral resistance and, hence, exert a favorable effect in angina pectoris or heart failure.

The heart muscle cells can also be reached directly. Thus, cardiac glycosides bind to the Na^+/K^+-ATPases, (p. 148), the Ca^{2+} antagonists to Ca^{2+} channels (p. 140), and antiarrhythmics of the local anesthetic type to Na^+ channels (p. 150) in the plasmalemma.

Levosimendan is a "calcium sensitizer" that can be used in acute heart failure to promote binding of Ca^{2+} to the myofilaments, thus increasing contractility. In addition, it has a vasodilating action and reduces pre- and afterload.

► **Events underlying contraction and relaxation of myocardial cells.** The signal-triggering **contraction** is a propagated action potential (AP) generated in the sinoatrial node (► Fig. 18.1B). *Depolarization* of the plasmalemma leads to opening of the L-type Ca^{2+} channels and then of the ryanodine receptors, Ca^{2+} channels in the sarcoplasmic reticulum. Ca^{2+} in the cytosol diffuses into the myofilaments to produce contraction of the cardiomyocyte (**electromechanical coupling**). During the action potential, the Na^+/Ca^{2+} exchanger moves more Ca^{2+} into the cell. The direction depends on the membrane potential as the Na^+/Ca^{2+} exchanger transports three Na^+ ions for one Ca^{2+} ion. When the membrane is depolarized, this exchange moves Ca^{2+} into the cell and moves it out again when the membrane is repolarized. The level of Ca^{2+} concentration attained in the cytosol determines the degree of shortening, i.e., the force of contraction.

The trigger signal for **relaxation** is the return of the membrane potential to its resting level. During repolarization Ca^{2+} levels fall below the threshold for activation of the myofilaments (3×10^{-7} M): Ca^{2+} ions are pumped back into the SR lumen by the sarcoplasmic Ca^{2+}-ATPase (SERCA). A smaller proportion of the Ca^{2+} is extruded from the cell by the plasmalemma *Ca^{2+}-ATPases* and the Na^+/Ca^{2+} *exchanger*.

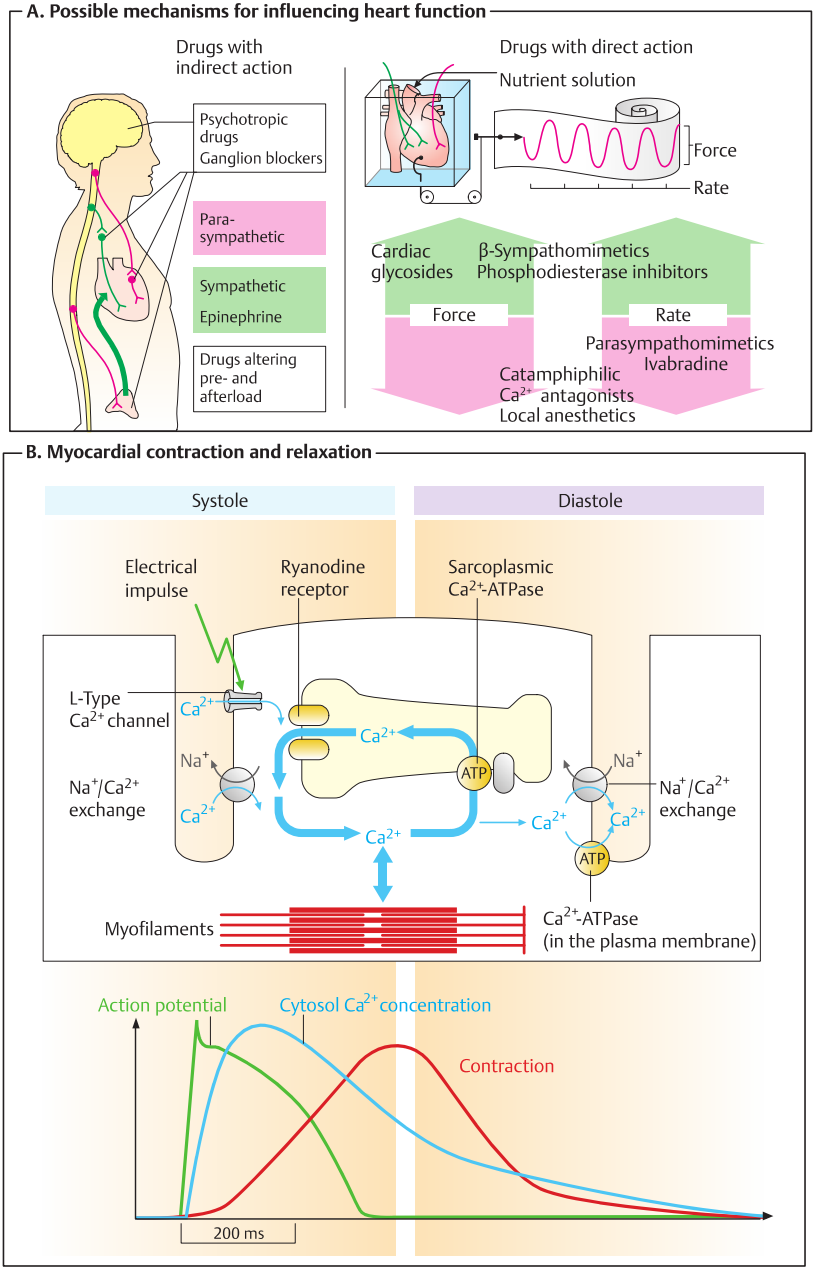

A. Possible mechanisms for influencing heart function
Drugs with indirect action
Psychotropic drugs
Ganglion blockers
Para-sympathetic
Sympathetic
Epinephrine
Drugs altering pre- and afterload
Drugs with direct action
Nutrient solution
Force
Rate
Cardiac glycosides
β-Sympathomimetics
Phosphodiesterase inhibitors
Force
Rate
Parasympathomimetics
Ivabradine
Catamphiphilic Ca2+ antagonists
Local anesthetics
B. Myocardial contraction and relaxation
Systole
Diastole
Electrical impulse
Ryanodine receptor
Sarcoplasmic Ca2+-ATPase
L-Type Ca2+ channel
Na+/Ca2+ exchange
Ca2+
Na+
ATP
Myofilaments
Ca2+-ATPase (in the plasma membrane)
Action potential
Cytosol Ca2+ concentration
Contraction
200 ms

Fig. 18.1

Cardiac Glycosides

Digoxin and Digitoxin

Diverse plants are sources of sugar-containing compounds (glycosides; see ▶ Fig. 18.2**A** for structural formulae) that augment the contractile force of heart muscle: *cardiotonic glycosides, cardiosteroids, "digitalis."* Digoxin and digitoxin are the most important cardiac glycosides; digoxin differs from digitoxin by an additional OH group (▶ Fig. 18.2**A**), which affects its pharmacokinetic properties. Enteral absorption of *digoxin* is variable and elimination is mainly renal, so there is a risk of accumulation with renal failure. *Digitoxin* is metabolized in the liver, conjugated with sulfate or glucuronate, and secreted into the bile. In the bowel it is deconjugated and reabsorbed. This *enterohepatic circulation* and the high plasma protein binding (>95%) are the reasons for digitoxin's very long plasma half-life (5–7 days). Treatment may start with an initial loading dose, followed by a lower oral maintenance dose.

Mechanism of Cardiac Glycoside Action

The cardiosteroids possess a small therapeutic margin; signs of intoxication are arrhythmia and contracture (▶ Fig. 18.2**B**).

Cardiac glycosides (**CG**) bind to the extracellular domain of Na^+/K^+-ATPases and exclude this enzyme molecule for a time from further ion transport activity. The ATPases maintain the transmembrane concentration gradients of Na^+/ K^+ and the negative resting potential and normal electrical excitability of the cell membrane. When some of the Na^+/K^+-ATPases are occupied and blocked by CG, the intracellular Ca^{2+} concentration rises, with an increase in contractile force.

The positive inotropic effect of the cardiac glycosides is explained by means of the following model (▶ Fig. 18.2**B**): inhibition of Na^+/K^+-ATPase leads initially to a slight rise in the intracellular Na^+ concentration in the vicinity of the cell membrane. This reduces the Na^+ gradient across the cell membrane, which acts as the driving force for the Na^+/ Ca^{2+} exchange transporter, and fewer Ca^{2+} ions are moved out of the cardiac muscle cell. The contractile force increases as a direct result.

Mobilization of edema (weight loss) and lowering of heart rate are simple but decisive criteria for achieving optimal dosing. If ATPase activity is inhibited too much, K^+ and Na^+ homeostasis is disturbed: the membrane potential declines, and extrasystoles and other *arrhythmias* occur due to late depolarization (▶ Fig. 18.2**B**). Intracellular flooding with Ca^{2+} prevents relaxation during diastole: *contracture.*

The **CNS effects** of CGs (▶ Fig. 18.2**C**) are also due to binding to Na^+/K^+-ATPases. Enhanced vagal nerve activity causes a decrease in sinoatrial beating rate and velocity of atrioventricular conduction. In patients with heart failure, improved circulation also contributes to the reduction in heart rate. Stimulation of the area postrema leads to nausea and vomiting (▶ Fig. 18.2**C**).

Indications for CGs are:

1. *chronic congestive heart failure;*
2. *atrial fibrillation or flutter,* where inhibition of AV conduction protects the ventricles from excessive atrial impulse activity and thereby improves cardiac performance (▶ Fig. 18.2**D**).

Signs of intoxication are:

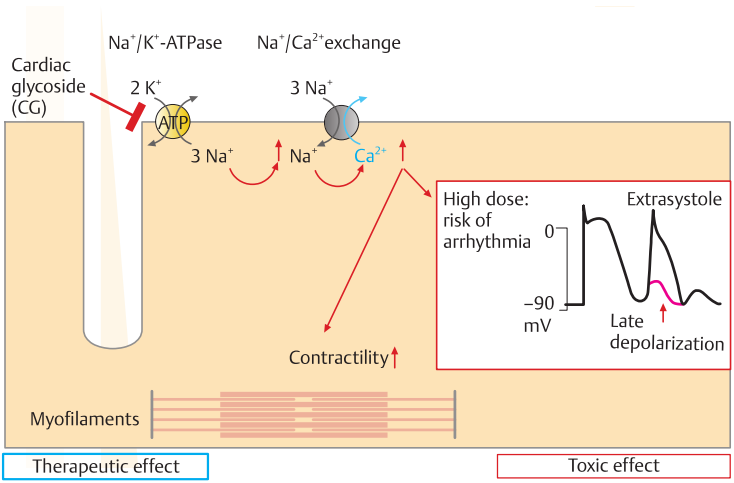
1. *Cardiac arrhythmias,* which under certain circumstances are life-threatening, e.g., sinus bradycardia, AV block, ventricular extrasystoles, ventricular fibrillation (ECG);
2. *CNS disturbances:* characteristically, altered color vision (xanthopsia), and also fatigue, disorientation, hallucinations;
3. anorexia, nausea, vomiting, diarrhea;
4. *renal:* loss of electrolytes and water; this must be differentiated from mobilization of edema fluid accumulated in front of the heart during congestive failure, an effect expected with therapeutic dosage.

Therapy of intoxication: *administration of K^+,* which reduces binding of CG but may impair AV conduction; administration of antiarrhythmics (p. 150). The most important measure is injection of *antibody (Fab) fragments* that bind and inactivate digitoxin and digoxin.

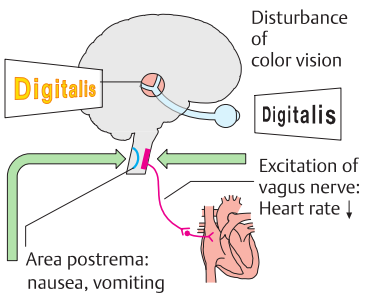
A. Cardiac glycosides

	Enteral absorption	Elimination	
Digoxin	~80%	$t_{1/2}$: 2–3 days Prolonged with decreased renal function	Better control
Digitoxin	100%	$t_{1/2}$: 5–7 days Independent of renal function	Slow waning of intoxication

B. Therapeutic and toxic effects of cardiac glycosides (CG)



C. Cardiac glycoside effects on the CNS



D. Cardiac glycoside effects in atrial fibrillation

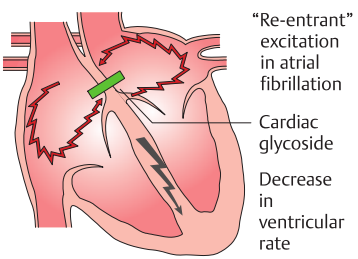


Fig. 18.2

Antiarrhythmic Drugs

Cardiac Impulse Generation and Conduction

The electrical impulse for cardiac contraction (propagated action potential; p. 136) originates in pacemaker cells of the sinoatrial node (▶ Fig. 18.3**A**1) and spreads through the atria (2), atrioventricular (AV) node (3), and adjoining parts of the His–Purkinje fiber system (4) to the ventricles (5). Irregularities of heart rhythm can have a dangerous effect on cardiac pumping function. Arrhythmias are managed by antiarrhythmic drugs and increasingly by pacemakers and invasive electrophysiologic procedures. Antiarrhythmic agents are traditionally grouped according to the Vaughan Williams classification:

- Class I: Na^+ channel blockers
- Class II: β-blockers (p. 116), the only antiarrhythmic agents that prolong life
- Class III: K^+ channel blockers
- Class IV: Ca^{2+} channel blockers (p. 140).

▶ **Action potential in the sinus and AV node (▶ Fig. 18.3B, C).** The pacemaker cells in the sinus and AV nodes are characterized by slow depolarization in diastole, which is mediated by hyperpolarization-activated cyclic nucleotide-gated (HCN) channels. When the membrane potential reaches its threshold, an action potential is triggered, followed by the next heart beat. *Ivabradine* is a specific HCN channel blocker that can be used to treat tachycardia. Autonomic regulation of heart rate is also via HCN channels, with readiness to open controlled by cAMP. Adrenergic stimulation of cardiac β-receptors increases the pacemaker current via G_s-protein, adenylyl cyclase, and cAMP (▶ Fig. 18.3**B, C**; green arrow, positive chronotropism). Acetylcholine reduces the heart rate through $G_{i/o}$-protein-coupled M_2 receptors, which inhibit adenylyl cyclase and open K^+ channels (▶ Fig. 18.3**B, C**; red arrow, negative chronotropism). *β-Blockers* can be given to treat sinus tachycardia, while *atropine* can be used for bradycardia. *Adenosine* can be injected intravenously in supraventricular tachycardia; it reduces the rate and diminishes AV conduction.

The action potential of the pacemaker cells is mediated by voltage-gated Ca^{2+} channels, which can be inhibited by cationic amphiphilic Ca^{2+} antagonists (p. 140), e.g., verapamil and diltiazem. Both are used to reduce rapid AV conduction in atrial fibrillation and flutter (p. 150).

▶ **Action potential in the working myocardium (▶ Fig. 18.3D).** Unlike the pacemaker cells, those of the working atrial and ventricular myocardium and the rest of the conducting tissue (blue in ▶ Fig. 18.3**A**) have a stable membrane potential in diastole. Action potentials are triggered via voltage-gated Na^+ channels and conducted to the neighboring myocardial cells through connexins in *gap junctions*. Depolarization is followed by a plateau phase, in which extracellular Ca^{2+} flows into the cell and triggers contraction (p. 146). Repolarization is initiated by opening of different K^+ channels. Na^+ and K^+ channels are important target proteins for antiarrhythmic drugs.

Antiarrhythmic Drugs

▶ **Na^+ channel blockers (▶ Fig. 18.3D).** Na^+ channel blockers reduce the velocity of the increase of the action potential, thereby reducing the speed of conduction. This can interrupt reentry impulses in the atrium and ventricle. These antiarrhythmics are divided into three groups:

- Class IA (action potential prolonged): quinidine (no longer on the market)
- Class IB (AP shortened): lidocaine; also used as a local anesthetic (p. 204)
- Class IC (AP unchanged): flecainide, propafenone.

Lidocaine binds only briefly to the Na^+ channel and therefore works especially at high heart rates ("use dependence"). Because of its low oral bioavailability, it is given intravenously to treat ventricular tachyarrhythmias. Class IC antiarrhythmics block Na^+ channels for much longer than lidocaine and can therefore also work at rest. They are used in atrial fibrillation to convert this to sinus rhythm and maintain it (p. 152). In principle, all class I antiarrhythmics can also have a proarrhythmic action.

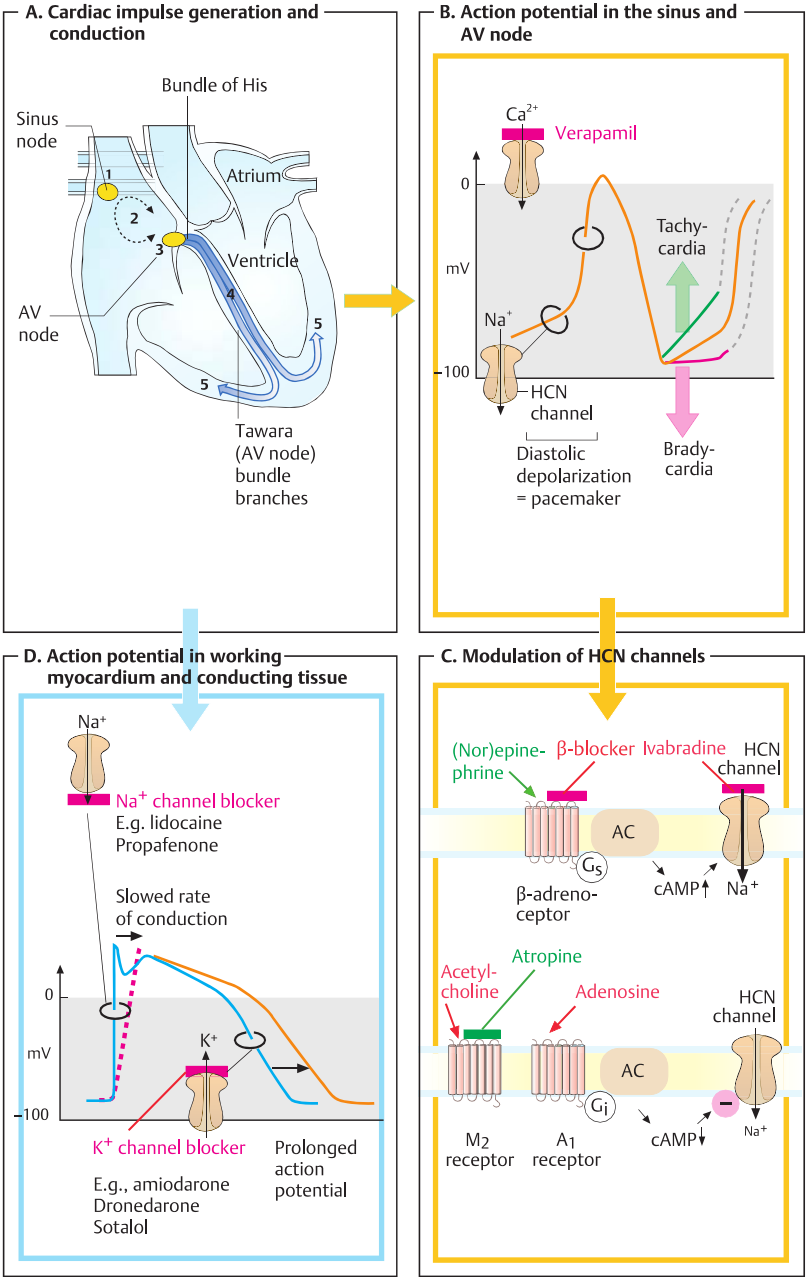

A. Cardiac impulse generation and conduction
Bundle of His
Sinus node
Atrium
Ventricle
AV node
Tawara (AV node) bundle branches
B. Action potential in the sinus and AV node
Ca2+
Verapamil
0
mV
−100
Na+
HCN channel
Tachy-cardia
Brady-cardia
Diastolic depolarization = pacemaker
C. Modulation of HCN channels
(Nor)epine-phrine
β-blocker
Ivabradine
HCN channel
AC
Gs
β-adreno-ceptor
cAMP
Na+
Acetyl-choline
Atropine
Adenosine
Gi
M2 receptor
A1 receptor
D. Action potential in working myocardium and conducting tissue
Na+ channel blocker
E.g. lidocaine
Propafenone
Slowed rate of conduction
K+
K+ channel blocker
E.g., amiodarone
Dronedarone
Sotalol
Prolonged action potential

Fig. 18.3

► **K^+ channel blockers** (► **Fig. 18.3C**). K^+ channel blockers delay repolarization of the action potential, thereby prolonging the refractory period until the cardiomyocytes can be excited again. This group includes amiodarone, dronedarone, sotalol, and vernakalant. *Sotalol* blocks β-adrenergic receptors in addition to K^+ channels. *Vernakalant* reduces the K^+ I_{KUR} current in the atrium and can be used intravenously for conversion of atrial fibrillation present less than 7 days.

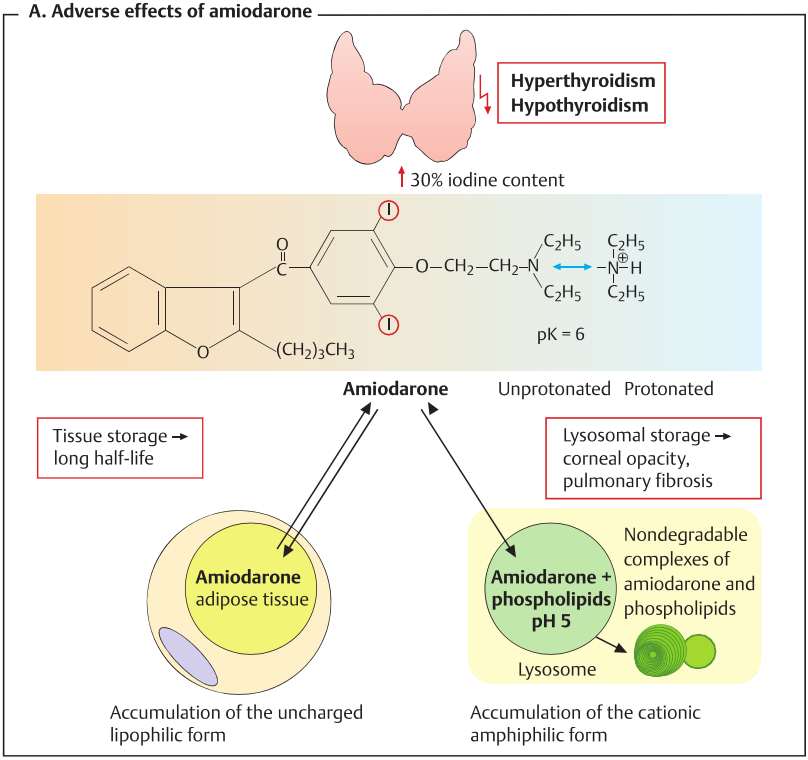
Amiodarone (► Fig. 18.4**A**) is the main antiarrhythmic K^+ channel blocker, though it can block a range of other channels and receptors (including adrenoceptors). It is an amphiphilic benzofurane derivative with two iodine atoms and its chemical properties result in pharmacological peculiarities that must be noted in treatment. There is pronounced tissue deposition so amiodarone is eliminated extremely slowly from the body ($t_{1/2}$ 30–50 days). In unprotonated form amiodarone is highly lipophilic and accumulates in adipose tissue. Amiodarone is protonated in the acid pH of the lysosomes and forms stable complexes with membrane phospholipids. On electron microscopy, these complexes are visible in many cells as onion-like inclusion bodies; in the cornea, for example, they are held responsible for visual disturbances. The iodine moiety can interfere with thyroid function, giving rise to both hyper- and hypothyroidism. Other adverse effects are photosensitization and, very rarely, pulmonary fibrosis. *Dronedarone* is an iodine-free derivative of amiodarone with a shorter half-life (25–30 h) and without the problems of tissue deposition and thyroid interference. However, its antiarrhythmic action is less than that of amiodarone. Because they prolong repolarization, class III antiarrhythmics can produce *Torsade-de-pointes arrhythmias*, which can progress to life-threatening ventricular fibrillation. For safety, the QT_C interval in the ECG must be monitored regularly.

Treatment of Atrial Fibrillation

Atrial fibrillation is the most common cardiac arrhythmia. It can result from structural damage to the atrial myocardium in various diseases (► Fig. 18.4**B**). Arrhythmogenic triggers in the pulmonary veins can trigger transient, more prolonged, or even permanent fibrillation due to reentry mechanisms in the atria. Electrical isolation of these triggers in the pulmonary veins by catheter ablation is a causal treatment. Since the fibrillating atrium no longer contracts in a coordinated manner, thrombi can form and the risk of embolism to the cerebral arteries causing stroke increases. The aims of atrial fibrillation treatment are as follows:

- Reduction of stroke risk
- Rate control
- Conversion to sinus rhythm (rhythm control).

The most important aim is prevention of stroke by giving anticoagulants (p. 160). Secondary aims are control of heart rate and rhythm. By acting as a filter, the AV node prevents atrial fibrillation from spreading to the ventricles, but ventricular pump function may be irregular ("absolute arrhythmia," no P wave in the ECG). Periods of fast AV conduction can lead to ventricular tachycardia with reduced ventricular filling and impaired pump function. Drugs that slow AV conduction (*β-blockers, digitalis glycosides, verapamil)* can help to limit the ventricular rate (target < 110/min). Measures to restore sinus rhythm ("rhythm control") are effective when the atrial fibrillation has not been present for long. Electrical conversion can be performed with a defibrillator under brief anesthesia. Alternatively, the following drugs can be used for conversion and for maintenance of sinus rhythm: *vernakalant* (i.v.), *flecainide, propafenone, sotalol, dronedarone*, or *amiodarone* (p.o.). Because of the potential proarrhythmic effects of the class I and III antiarrhythmics, the benefit and risk should be considered carefully, especially in the case of structural heart disease. Innovative pacemakers and invasive catheter procedures may support or replace prolonged pharmacotherapy.


A. Adverse effects of amiodarone
Hyperthyroidism
Hypothyroidism
30% iodine content
I
O
C
O–CH2–CH2–N
C2H5
C2H5
–N–H
C2H5
C2H5
I
O
(CH2)3CH3
pK = 6
Amiodarone
Unprotonated Protonated
Tissue storage → long half-life
Lysosomal storage → corneal opacity, pulmonary fibrosis
Amiodarone adipose tissue
Amiodarone + phospholipids pH 5
Nondegradable complexes of amiodarone and phospholipids
Lysosome
Accumulation of the uncharged lipophilic form
Accumulation of the cationic amphiphilic form

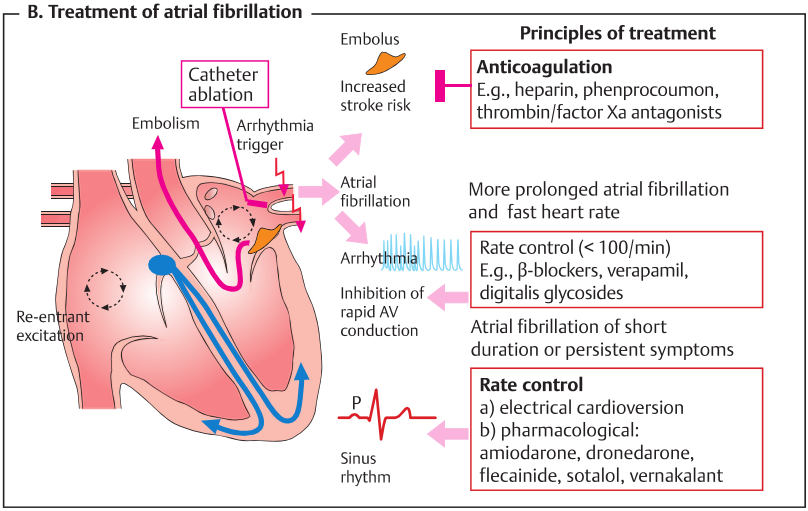

B. Treatment of atrial fibrillation
Principles of treatment
Catheter ablation
Embolism
Arrhythmia trigger
Re-entrant excitation
Embolus
Increased stroke risk
Anticoagulation
E.g., heparin, phenprocoumon, thrombin/factor Xa antagonists
Atrial fibrillation
More prolonged atrial fibrillation and fast heart rate
Arrhythmia
Inhibition of rapid AV conduction
Rate control (< 100/min)
E.g., β-blockers, verapamil, digitalis glycosides
Atrial fibrillation of short duration or persistent symptoms
P
Sinus rhythm
Rate control
a) electrical cardioversion
b) pharmacological:
amiodarone, dronedarone, flecainide, sotalol, vernakalant

Fig. 18.4

Drugs for the Treatment of Anemias

Anemia denotes a reduction in red blood cell count or hemoglobin content, or both.

► **Erythropoiesis** (► **Fig. 19.1A**). Red blood cells (erythrocytes) develop from stem cells through several cell divisions (n = 17!). Hemoglobin is then synthesized and the cell nucleus is extruded. Erythropoiesis is stimulated by the hormone **erythropoietin** (a glycoprotein), which is released from the kidneys when renal oxygen tension declines. Nephrogenic anemia can be ameliorated by parenteral administration of recombinant erythropoietin (epoetin alfa) or hyperglycosylated erythropoietin (darbepoetin; longer half-life than epoetin). For further information about the epoetins and other activators of blood cell formation, see Stimulation of blood cell formation (p. 168).

Even in healthy humans, formation of red blood cells and, hence, the oxygen transport capacity of blood, is augmented by erythropoietin. This effect is equivalent to high-altitude training and is employed as a doping method by high-performance athletes. Erythropoietin is inactivated by cleavage of sugar residues with a biological half-life of ~5 hours after intravenous injection and a $t_{1/2}$ >20 hours after subcutaneous injection.

Given adequate production of erythropoietin, a **disturbance of erythropoiesis** is due to two principal causes. (1) **Cell multiplication** is **inhibited** because DNA synthesis is insufficient. This occurs in deficiencies of *vitamin B_{12}* or *folic acid* (macrocytic hyper-chromic anemia). (2) **Hemoglobin synthesis** is **impaired**. This situation arises in **iron deficiency**, since Fe^{2+} is a constituent of hemoglobin (microcytic hypochromic anemia).

Vitamin B_{12}

Vitamin B_{12} (**cyanocobalamin,** ► Fig. 19.1**B**) is produced by bacteria; vitamin B_{12} generated in the colon, however, is unavailable for absorption. Liver, meat, fish, and milk products are rich sources of the vitamin. The **minimal requirement** is about 1 µg/day. Enteral absorption of vitamin B_{12} requires the so-called **"intrinsic factor"** from parietal cells of the stomach. The complex formed with this glycoprotein undergoes endocytosis in the ileum. Bound to its transport protein, transcobalamin, vitamin B_{12} is destined for storage in the liver or uptake into tissues.

A frequent cause of **vitamin B_{12} deficiency** is atrophic gastritis leading to a *lack of intrinsic factor*. Besides megaloblastic anemia, damage to mucosal linings and degeneration of myelin sheaths with neurological sequelae will occur (**pernicious anemia**). The **therapy** consists in **parenteral administration** of **cyanocobalamin** or **hydroxycobalamin** (vitamin B_{12a}; exchange of –CN for –OH group).

Folic Acid

Leafy vegetables and liver are rich in folic acid (FA) (► Fig. 19.1**B**). The **minimal requirement** is ~50 µg/day. Polyglutamine-FA in food is hydrolyzed to monoglutamine-FA prior to being absorbed. **Causes of deficiency** include insufficient intake, malabsorption (a side effect of many drugs), and increased requirement during pregnancy. In the first weeks of pregnancy, FA deficiency can cause neural tube defects in the embryo. For this reason, FA prophylaxis should begin prior to conception if possible. At later stages, such defects can no longer be corrected by taking FA. *Symptoms* of deficiency otherwise are megaloblastic anemia and mucosal damage. **Therapy** consists in **oral administration** of FA.

Administration of FA can mask a vitamin B_{12} deficiency. Vitamin B_{12} is required for the conversion of methyltetrahydro-FA to tetrahydro-FA, which is important for DNA synthesis (► Fig. 19.1**B**). Inhibition of this reaction due to vitamin B_{12} deficiency can be compensated by increased FA intake. The anemia is readily corrected; however, nerve degeneration progresses unchecked and its cause is made more difficult to diagnose by the absence of hematological changes. Indiscriminate use of FA-containing multivitamin preparations can, therefore, be harmful.

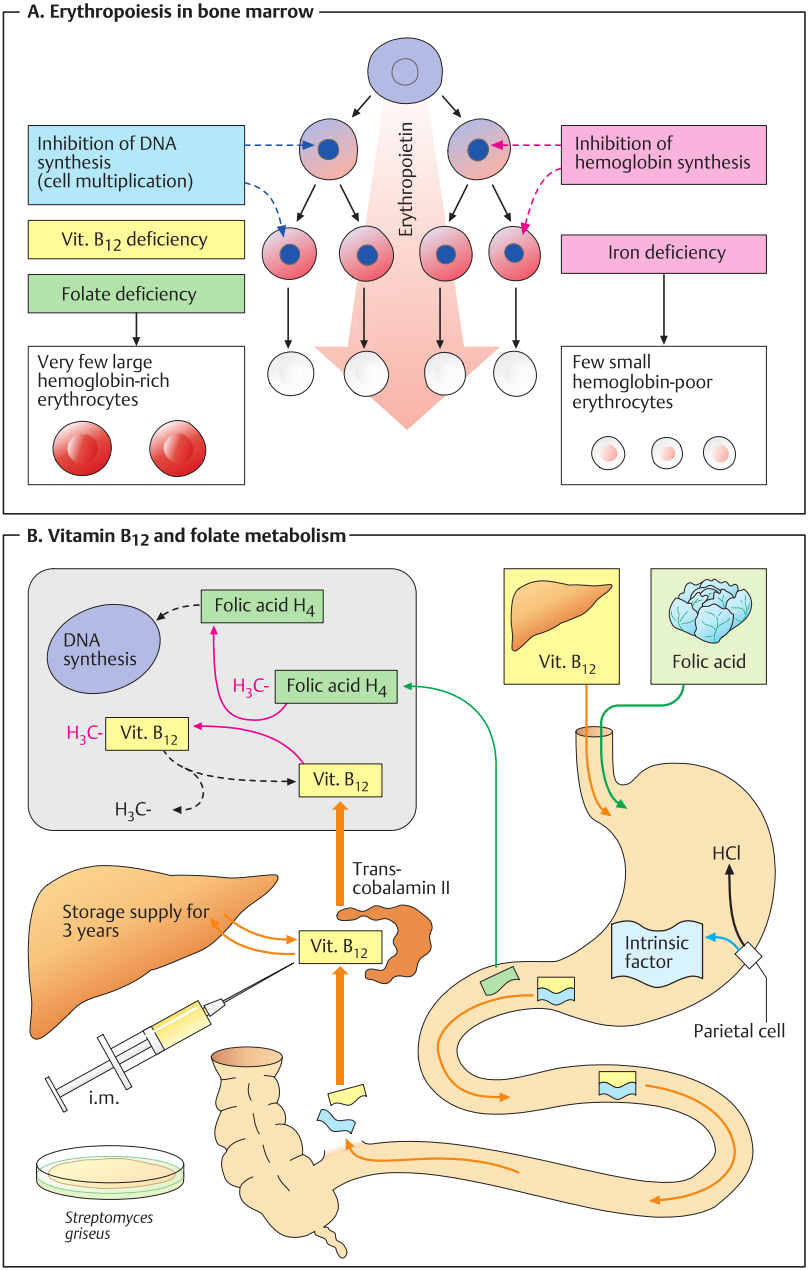

A. Erythropoiesis in bone marrow
Inhibition of DNA synthesis (cell multiplication)
Vit. B12 deficiency
Folate deficiency
Very few large hemoglobin-rich erythrocytes
Erythropoietin
Inhibition of hemoglobin synthesis
Iron deficiency
Few small hemoglobin-poor erythrocytes
B. Vitamin B12 and folate metabolism
DNA synthesis
Folic acid H4
H3C-
Folic acid H4
H3C-
Vit. B12
Vit. B12
H3C-
Vit. B12
Folic acid
HCl
Trans-cobalamin II
Storage supply for 3 years
Vit. B12
Intrinsic factor
Parietal cell
i.m.
Streptomyces griseus

Fig. 19.1

Iron Deficiency Anemia

Dietary iron is ingested in different forms: as trivalent Fe(III), which cannot be absorbed by the small intestinal mucosa; as divalent Fe(II), which is absorbable; and finally as bound heme iron. This iron complex (hemoglobin, myoglobin) is absorbed particularly effectively from the intestine and probably represents the physiological source throughout human history before inorganic iron compounds made their way into the kitchen in the "iron age."

There is a special **transporter protein for heme** iron in the apical enterocyte membrane. Followingendocytosis of this complex, Fe(II) is liberated by a **heme oxygenase**, and this can then leave the basolateral part of the cell via the transporter **ferroportin**.

An apical **divalent metal transporter** is available for the absorption of Fe(II) ions. This moves Fe(II) into the cytosol and, like the Fe(II) derived from heme, it exits the enterocytes by means of ferroportin. On the membrane surface, it is oxidized to Fe(III) by **hephaestin** and is subsequently bound to **transferrin**, the iron transport protein in the body.

Enteral absorption of iron is subject to negative feedback: only as much iron as necessary is absorbed. The amount of ferroportin available to export iron from the enterocytes is the controlling step. This is determined by **hepcidin**, which increases or reduces the number of available ferroportin units; this results in the so-called **mucosal block** (which protects against oral iron overload).

A frequent **cause of iron deficiency** is chronic blood loss due to gastric/intestinal ulcers or tumors. One liter of blood contains 500 mg of iron in healthy condition. Despite a significant increase in absorption rate, absorption is unable to keep up with losses and the body store of iron falls. Iron deficiency results in impaired synthesis of hemoglobin and **anemia**.

The **treatment** of choice (after the cause of bleeding has been found and eliminated) consists in the **oral administration of Fe^{2+} compounds**, e.g., ferrous sulfate (daily dose 100 mg of iron, equivalent to 300 mg of $FeSO_4$, divided into multiple doses). Replenishing of iron stores may take several months. Oral administration, however, is advantageous in that it is impossible to overload the body with iron through an intact mucosa because of its demand-regulated absorption (mucosal block).

Adverse effects. The frequent gastrointestinal complaints (epigastric pain, diarrhea, constipation) necessitate intake of iron preparations with or after meals, although absorption is higher from the empty stomach.

Interactions. Antacids inhibit iron absorption. Combination with ascorbic acid (vitamin C) to protect Fe^{2+} from oxidation to Fe^{3+} is theoretically sound but practically is not needed.

Parenteral administration of Fe^{3+} salts is indicated only when adequate oral replacement is not possible. There is a risk of overdosage, with iron deposition in tissues (**hemosiderosis**). The binding capacity of transferrin is limited and free Fe^{3+} is toxic. Therefore, Fe^{3+} complexes are employed that can donate Fe^{3+} directly to transferrin or can be phagocytosed by macrophages, enabling iron to be incorporated into the ferritin store. Possible *adverse effects* are: with i.m. injection, persistent pain at the injection site and skin discoloration; with i.v. injection, flushing, hypotension, anaphylactic shock.

A practical aspect of treatment of iron deficiency anemia with oral iron preparations alluded to above should be noted. The required daily dosage is **100–200mg Fe^{2+}.** Iron cannot be provided as an isolated ion but is always present in bound form: as iron sulfate, iron succinate, iron gluconate, etc. In ferrous sulfate and ferrous succinate, Fe^{2+} accounts for about one-third of the drug weight, but in ferrous gluconate it accounts for only about one-eighth. Thus, if 100 mg Fe^{2+} is required, 300 mg ferrous sulfate or 800 mg ferrous gluconate must be prescribed.

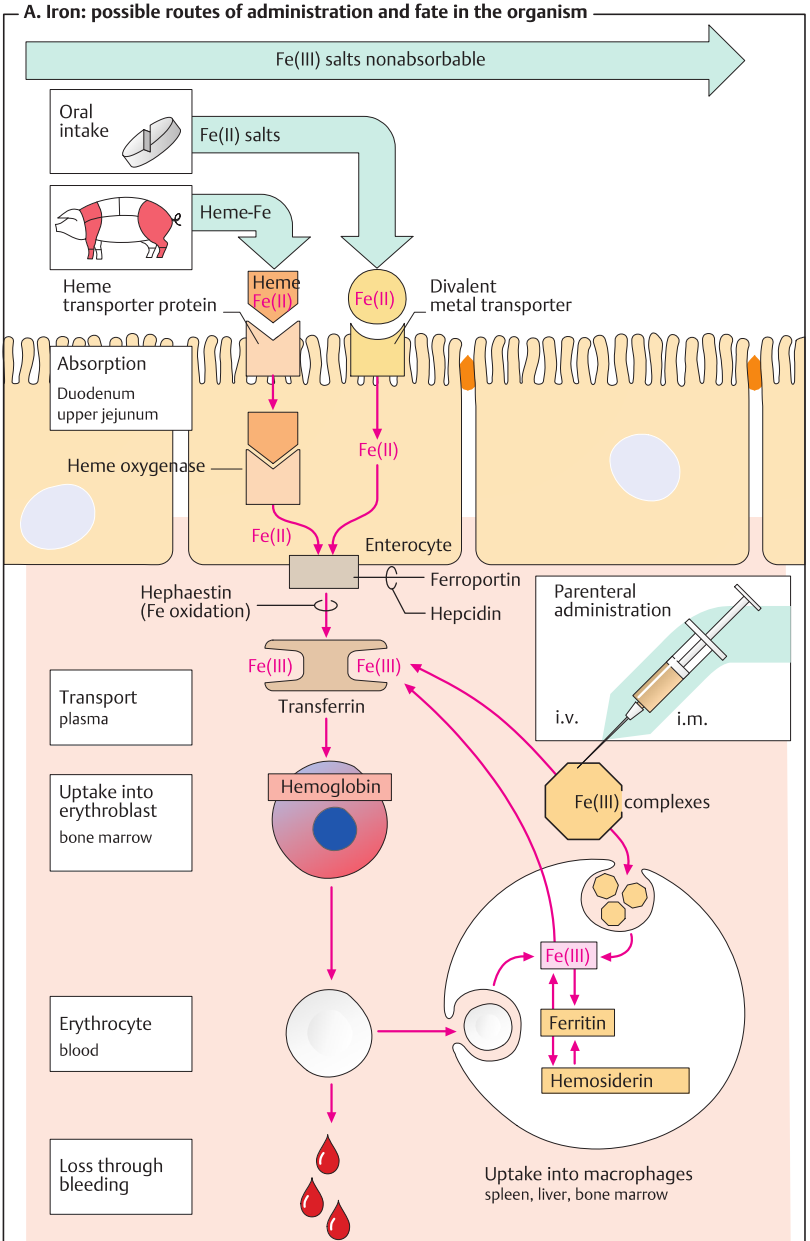

A. Iron: possible routes of administration and fate in the organism
Fe(III) salts nonabsorbable
Oral intake
Fe(II) salts
Heme-Fe
Heme transporter protein
Heme Fe(II)
Fe(II)
Divalent metal transporter
Absorption
Duodenum
upper jejunum
Heme oxygenase
Fe(II)
Fe(II)
Enterocyte
Ferroportin
Hepcidin
Hephaestin (Fe oxidation)
Parenteral administration
i.v.
i.m.
Fe(III)
Fe(III)
Transferrin
Transport
plasma
Hemoglobin
Fe(III) complexes
Uptake into erythroblast
bone marrow
Fe(III)
Ferritin
Hemosiderin
Erythrocyte
blood
Loss through bleeding
Uptake into macrophages
spleen, liver, bone marrow

Fig. 19.2

Prophylaxis and Therapy of Thrombosis

Upon vascular injury, platelet aggregation and the coagulation system are activated (▶ Fig. 20.1A): platelets and fibrin molecules coalesce into a "plug" that seals the defect and halts bleeding (**hemostasis**). Unnecessary formation of an intravascular clot—a thrombosis—can be life-threatening. If the clot forms on an atheromatous plaque in a coronary artery, myocardial infarction is imminent; a thrombus in a deep leg vein can be dislodged and carried into a lung artery and can cause pulmonary embolism; in atrial fibrillation, thrombi can form in the atria, which are then carried to cerebral arteries, precipitating a stroke.

Drugs that *decrease the coagulability of blood,* such as **coumarins** and **heparin**, are employed for thrombosis **prophylaxis**. Other drugs inhibit the aggregation of blood platelets, which are prominently involved in intra-arterial thrombogenesis (p. 166). For the **therapy** of thrombosis, drugs are used that dissolve the fibrin meshwork—**fibrinolytics**, that is, plasminogen activators (p. 164).

Following endothelial injury, platelets circulating in the blood adhere to the exposed extracellular matrix, where they are quickly activated and aggregate into a still labile clump within a few minutes (▶ Fig. 20.1A). This process is called **primary hemostasis**. If vascular cells or tissue cells that contain tissue factor (TF) in their cell membrane are exposed, **secondary hemostasis** starts. Numerous proteins of the plasma clotting system are involved, some of which interact with the platelet clumps and then close the vessel injury with a fibrin thrombus, which is stabilized by factor XIIIa.

The **clotting factors** are protein molecules, which—apart from fibrin and cofactors Va and VIIa—are converted to active proteases by cleavage of protein fragments. Some activated factors, including the vitamin K-dependent factors II, VII, IX, and X, require the presence of phospholipids (PI) and Ca^{2+} ions for their proteolytic activity. Activation of the clotting cascade mediated by tissue factor complexed with factor VIIa predominates in the body. This used to be called the "extrinsic system." The "intrinsic system," which is initiated by factor XIIa, can be activated by negatively charged endogenous (e.g., collagen) or exogenous (e.g., glass, kaolin) surfaces.

Hereditary clotting disorders such as hemophilia can be treated by replacement with factors derived from human plasma or recombinant factors, e.g., octocog alfa, turoctocog alfa.

In vivo, the progression of hemostasis can be inhibited as follows (▶ Fig. 20.1A):

1. **Anti-platelet drugs (inhibitors of platelet aggregation)**, e.g., acetylsalicylic acid or clopidogrel, prevent the formation of a platelet-rich thrombus. They act especially in the arterial system and are used, for example, in the prevention and treatment of myocardial infarction (p. 328).
2. **Direct inhibitors** of the coagulation cascade inhibit the protease activity of factors Xa and IIa (thrombin).
3. **Indirect factor Xa/IIa inhibitors** act by increasing the physiological inhibitor antithrombin (see heparins; p. 162), and coumarin derivatives (p. 160) reduce synthesis of the γ-carboxylated activatable factors II, VII, IX, and X by inhibiting their carboxylation in the liver.

In the treatment of thrombosis, it is necessary to distinguish between arterial and venous thrombosis. Arterial thrombi are platelet aggregations on mural defects, whereas venous thrombi are fibrin meshes that arise in sites where blood flow is slow or stagnant.

▶ **Direct inhibitors of the coagulation cascade (▶ Fig. 20.1B). Rivaroxaban**, apixaban and edoxaban are selective and reversible inhibitors of activated factor Xa. Specific thrombin inhibition can be obtained with **dabigatran**, which is given as the inactive ester precursor. These inhibitors are used for deep vein thrombosis prophylaxis after hip and knee joint replacement and for stroke prevention in patients with atrial fibrillation. Since elimination of dabigatran is predominantly via the kidney, renal function must be monitored as the plasma levels and hence the bleeding risk can rise with renal failure. The polypeptide **hirudin** from the saliva of the European medicinal leech inhibits clotting of the leech's blood meal by blockade of the active center of thrombin. **Lepirudin** and **bivalirudin** are genetically engineered analogues. They can be used in patients with heparin-induced thrombocytopenia (HIT II; p. 162) or acute coronary syndrome.

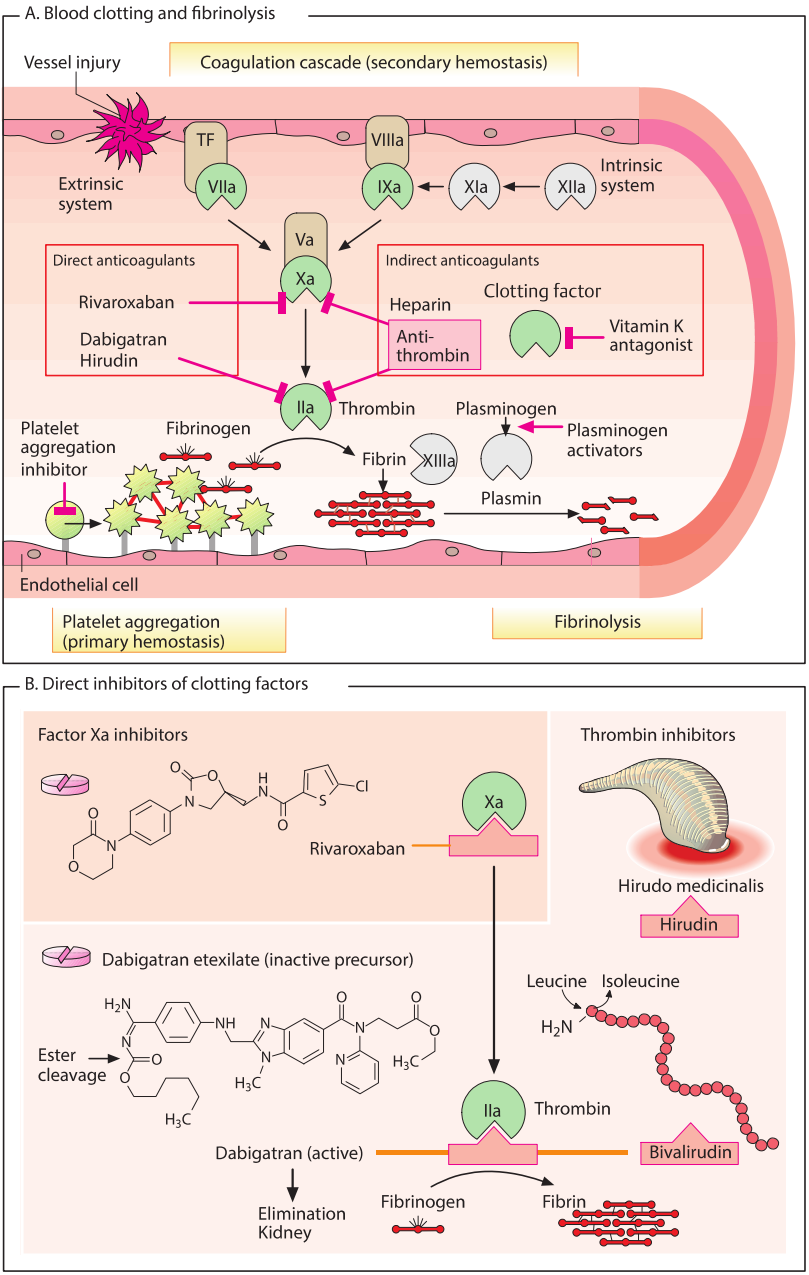

A. Blood clotting and fibrinolysis
Vessel injury
Coagulation cascade (secondary hemostasis)
TF
VIIa
VIIIa
IXa
XIa
XIIa
Intrinsic system
Extrinsic system
Va
Xa
Direct anticoagulants
Rivaroxaban
Dabigatran
Hirudin
Indirect anticoagulants
Heparin
Anti-thrombin
Clotting factor
Vitamin K antagonist
IIa
Thrombin
Plasminogen
Plasminogen activators
Platelet aggregation inhibitor
Fibrinogen
Fibrin
XIIIa
Plasmin
Endothelial cell
Platelet aggregation (primary hemostasis)
Fibrinolysis
B. Direct inhibitors of clotting factors
Factor Xa inhibitors
Rivaroxaban
Xa
Thrombin inhibitors
Hirudo medicinalis
Hirudin
Dabigatran etexilate (inactive precursor)
Ester cleavage
Leucine
Isoleucine
IIa
Thrombin
Dabigatran (active)
Bivalirudin
Elimination Kidney
Fibrinogen
Fibrin

Fig. 20.1

▶ **Inhibition of synthesis of vitamin K-dependent clotting factors. Vitamin K** promotes the hepatic γ-carboxylation of glutamate residues on the precursors of clotting factors II, VII, IX, and X (▶ Fig. 20.2**A**). Vitamin K is a cofactor of the enzyme γ-glutamyl carboxylase and is oxidized during the reaction to vitamin K epoxide. The carboxyl groups are required for Ca^{2+}-mediated binding to phospholipid surfaces and for maximal activation of blood clotting. Vitamin K epoxide is converted back to vitamin K hydroquinone by vitamin K epoxide reductase in two steps so it is again available as cofactor. There are several vitamin K derivatives of different origins: K_1 (phytomenadione) from chlorophyllous plants; K_2 from gut bacteria; and K_3 (menadione) synthesized chemically. All are hydrophobic and require bile acids for absorption from the gut.

Oral anticoagulants. Structurally related to vitamin K, **4-hydroxycoumarins** act as "false" vitamin K. They inhibit vitamin K epoxide reductase to produce a deficiency of active vitamin K. The hydroxycoumarins include phenprocoumon (elimination half-life 2–5 days) as well as warfarin (half-life 1–2 days) and acenocoumarol (2–6h).

Coumarins are well absorbed after oral administration. Their duration of action varies considerably. Synthesis of clotting factors depends on the intrahepatocytic concentration ratio between coumarins and vitamin K. The dose required for an adequate anticoagulant effect must be determined individually for each patient. Treatment is monitored by measuring the International Normalized Ratio, or INR.

▶ **Indications.** Hydroxycoumarins are used for the prophylaxis of thromboembolism as, for instance, in atrial fibrillation or after heart valve replacement.

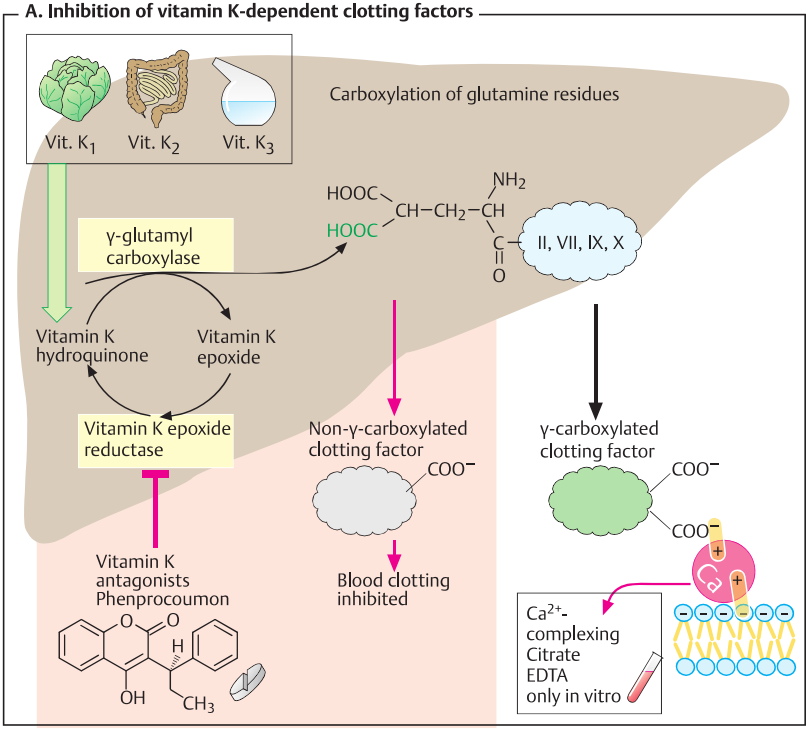
The **most important adverse effect is bleeding**. With coumarins, this can be counteracted by giving vitamin K_1. However, coagulability of blood returns to normal only after hours or days, when the liver has resumed synthesis and restored sufficient blood levels of carboxylated clotting factors. In urgent cases, deficient factors must be replenished directly (e.g., by transfusion of whole blood or of prothrombin concentrate).

Other notable adverse effects include: at the start of therapy, hemorrhagic skin necrosis and alopecia; with exposure in utero, disturbances of fetal cartilage and bone formation and CNS injury (due to bleeding); enhanced risk of retroplacental bleeding.

Interaction with Drugs and Foodstuffs

Adjusting the dosage of a hydroxycoumarin calls for a delicate balance between the opposing risks of bleeding (effect too strong) and of thrombosis (effect too weak) (▶ Fig. 20.2**B**). After the dosage has been titrated successfully, loss of control may occur if certain interfering factors are ignored. If the patient changes dietary habits and consumes more vegetables, vitamin K may predominate over the vitamin K antagonist. If vitamin K-producing gut flora is damaged in the course of antibiotic therapy, the antagonist may prevail. Drugs that increase hepatic biotransformation via enzyme induction (p. 54) may accelerate elimination of a hydroxycoumarin and thus lower its blood level. Inhibitors of hepatic biotransformation (e.g., azole antifungal agents) augment the action of hydroxycoumarins. Apart from pharmacokinetic alterations, pharmacodynamic interactions must be taken into account. Thus, acetylsalicylic acid is contraindicated because (a) it retards hemostasis by inhibiting platelet aggregation and (b) it may cause damage to the gastric mucosa with erosion of blood vessels.

Vitamin K antagonists are very effective drugs. In chronic atrial fibrillation, they reduce the risk of stroke by up to 60%. The correct dosage can be monitored using the INR laboratory test. Vitamin K and factor concentrate are available as antidotes in the event of overdose or bleeding. Due to the many possible interactions (▶ Fig. 20.2**B**), however, only 50–60% of patients are on the correct dose. Further clinical studies must demonstrate whether the direct thrombin and factor Xa inhibitors have a better benefit–risk profile (p. 158).


A. Inhibition of vitamin K-dependent clotting factors
Vit. K1
Vit. K2
Vit. K3
Carboxylation of glutamine residues
HOOC
CH–CH2–CH
HOOC
NH2
C
O
II, VII, IX, X
γ-glutamyl carboxylase
Vitamin K hydroquinone
Vitamin K epoxide
Vitamin K epoxide reductase
Non-γ-carboxylated clotting factor
COO−
γ-carboxylated clotting factor
COO−
COO−
Ca2+
Vitamin K antagonists Phenprocoumon
O
O
H
OH
CH3
Blood clotting inhibited
Ca2+-complexing
Citrate
EDTA
only in vitro

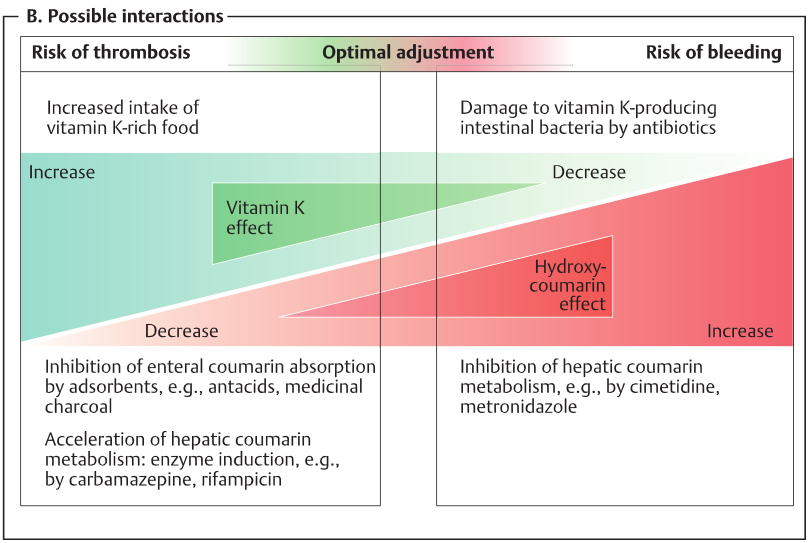

B. Possible interactions
Risk of thrombosis
Optimal adjustment
Risk of bleeding
Increased intake of vitamin K-rich food
Damage to vitamin K-producing intestinal bacteria by antibiotics
Increase
Decrease
Vitamin K effect
Hydroxy-coumarin effect
Decrease
Increase
Inhibition of enteral coumarin absorption by adsorbents, e.g., antacids, medicinal charcoal
Acceleration of hepatic coumarin metabolism: enzyme induction, e.g., by carbamazepine, rifampicin
Inhibition of hepatic coumarin metabolism, e.g., by cimetidine, metronidazole

Fig. 20.2

Heparin

► **Occurrence and structure.** Heparin (► Fig. 20.3**A**) can be obtained from porcine gut, where it is present (together with histamine) in storage vesicles of mast cells. Heparin molecules are chains of amino sugars bearing -COO^- and -SO_3^- groups. Chain length is not constant and anticoagulant efficacy varies with chain length. The potency of a preparation is standardized in international units of activity (IU) by bioassay and comparison with a reference preparation. The molecular weight (MW) for *unfractionated standard heparin* ranges from 4000 to 40 000, with a peak around 15 000. *Low-molecular-weight fractionated heparin* can be produced by cleavage of native heparin; molecular size is less heterogeneous, with a mean MW of 5000 (e.g., certoparin, dalteparin, enoxaparin). The synthetic *fondaparinux* (MW 1728) resembles the basic pentasaccharide subunit of heparin, essential for activity. The numerous negative charges are significant in several respects:

1. they contribute to complex formation with antithrombin III that underlies the anticoagulant effect;
2. they permit binding of heparin to its antidote, protamine (a polycationic protein from salmon sperm);
3. they confer poor membrane penetrability, necessitating administration of heparin by injection.

► **Mechanism of action.** *Antithrombin* is a circulating glycoprotein capable of inhibiting activated clotting factors by occupation and irreversible blockade of the active center. Heparin acts to inhibit clotting by accelerating formation of this complex more than 1000-fold. To inactivate thrombin, the heparin molecule must simultaneously contact the factor and antithrombin. With factor Xa, however, contact between heparin and antithrombin is sufficient for speeding up inactivation.

► **Indications.** Heparin is used for the prophylaxis and therapy of thrombosis. For the former, low dosages, given subcutaneously, are sufficient. Unfractionated heparin must be injected about three times daily; fractionated heparins and fondaparinux can be administered once daily. For treatment of thrombosis, heparin must be infused intravenously in an increased daily dose. When unfractionated heparin is used during surgery (e.g., for anticoagulation when a heart-lung machine is used) or during cardiac catheterization, its effect can be fully abolished by protamine at the end of the procedure. The effect of low-molecular-weight heparins or fondaparinux is poorly reversible with protamine.

► **Adverse effects.** Bleeding events must be anticipated during treatment with heparin. Heparin-induced thrombocytopenia type II (HIT II) is another dangerous complication (► Fig. 20.3**A**). It results from formation of antibodies that precipitate with bound heparin on platelets. The platelets aggregate and give rise to vascular occlusions. Because of the thrombocytopenia, hemorrhages may occur. The risk of HIT II is about 10 times greater after use of unfractionated heparin than after low-molecular-weight heparins or fondaparinux. If HIT II occurs, heparin must be stopped immediately and treatment can be continued with a hirudin derivative (p. 158).

The drug *danaparoid* consists mostly of the **heparinoid** heparan sulfate. Its chains are composed of a part of the heparin molecule (indicated by blue color underlay). Its effect is mediated by antithrombin.

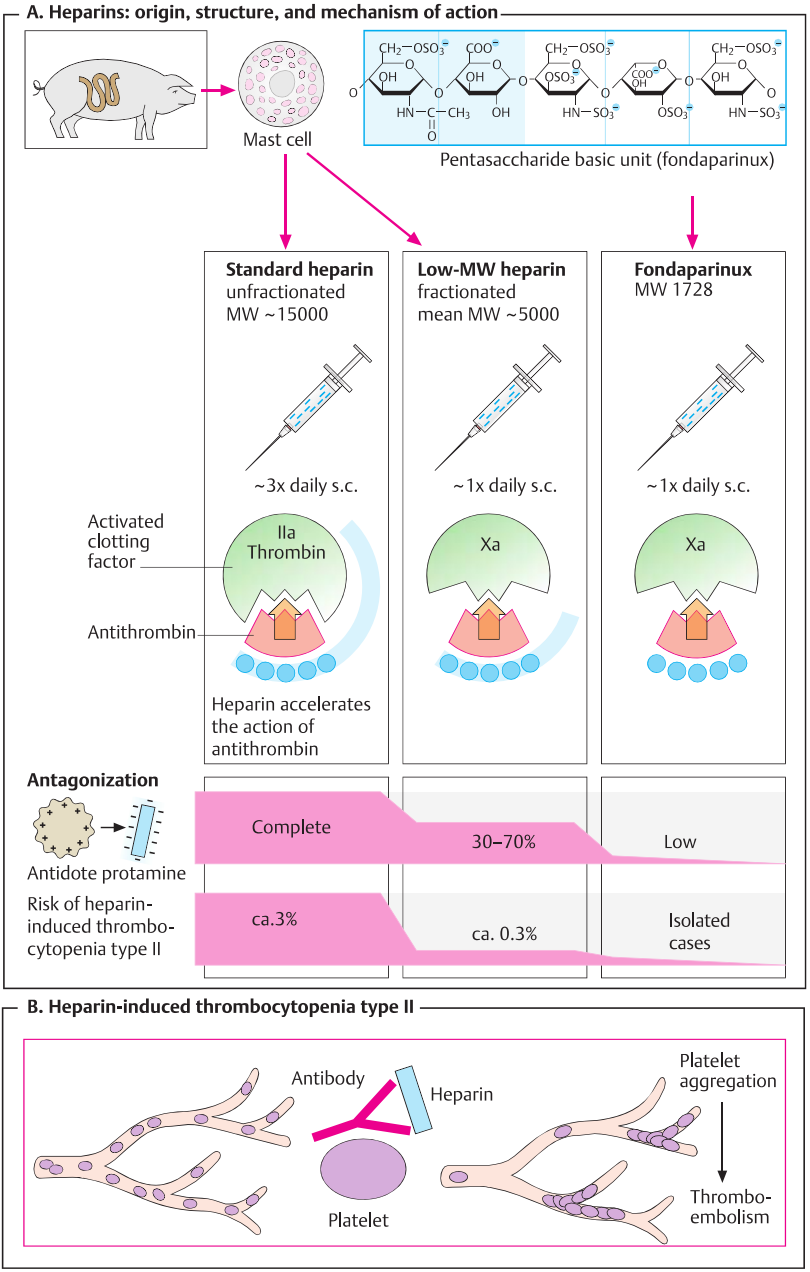

A. Heparins: origin, structure, and mechanism of action
Mast cell
Pentasaccharide basic unit (fondaparinux)
Standard heparin
unfractionated
MW ~15000
Low-MW heparin
fractionated
mean MW ~5000
Fondaparinux
MW 1728
~3x daily s.c.
~1x daily s.c.
~1x daily s.c.
Activated clotting factor
Antithrombin
IIa Thrombin
Xa
Xa
Heparin accelerates the action of antithrombin
Antagonization
Antidote protamine
Risk of heparin-induced thrombocytopenia type II
Complete
30–70%
Low
ca.3%
ca. 0.3%
Isolated cases
B. Heparin-induced thrombocytopenia type II
Antibody
Heparin
Platelet
Platelet aggregation
Thrombo-embolism

Fig. 20.3

Fibrinolytics

The fibrin meshwork of a blood clot can be cleaved by plasmin. As a protease, plasmin can break down not only fibrin but also fibrinogen and other proteins. Plasmin derives from an inactive precursor, plasminogen, present in blood. Under physiological conditions, specificity of action for fibrin is achieved because, among other things, activation takes place on the fibrin clot.

The **tissue plasminogen activator** (**t-PA**) is released into the blood from endothelial cells when blood flow stagnates. Next to its catalytic center, this protease possesses other functional domains, including docking sites for fibrin. During contact with fibrin, plasminogen–plasmin conversion rate is several-fold higher than in streaming blood. Plasminogen also contains a binding domain for fibrin.

Plasminogen activators available for therapeutic use are designated as fibrinolytics; they are infused intravenously in myocardial infarction, stroke, deep leg vein thrombosis, pulmonary embolism, and other thrombotic vascular occlusions. The earlier treatment is started after thrombus formation, the better is the chance of achieving patency of the occluded vessel.

The desired effect carries with it the risk of bleeding as the most important **adverse effect** because, apart from the intravascular fibrin clot forming the thrombus, other fibrin coagula-sealing defects in the vascular wall are dissolved as well. Moreover, use of fibrinolytics entails the risk that fibrinogen and other clotting factors circulating in blood will undergo cleavage ("systemic lytic state").

Streptokinase is the oldest available fibrinolytic. By itself it lacks enzymatic activity; only after binding to a plasminogen molecule is a complex formed that activates plasminogen. Streptokinase is produced by streptococcal bacteria. Streptokinase antibodies may be present as a result of previous streptococcal infections and may lead to incompatibility reactions.

Urokinase is an endogenous plasminogen activator that occurs in different organs. Urokinase used therapeutically is obtained from human cultured kidney cells. Circulating antibodies are not expected. The substance is more expensive than streptokinase and also does not depend on fibrin for its action.

Alteplase is a recombinant tissue plasminogen activator (rt-PA). As a result of its production in eukaryotic Chinese hamster ovary (CHO) cells, carbohydrate residues are present as in the native substance. At the therapeutically used dosage, alteplase loses its "fibrin dependence" and thus also activates circulating plasminogen. In fresh myocardial infarctions, alteplase appears to produce better results than does streptokinase.

Tenecteplase is a variant of alteplase that has been altered by six point mutations, resulting in a significant prolongation of its plasma half-life (tenecteplase $t_{1/2}$ = 20 minutes; alteplase $t_{1/2}$ = 3–4 minutes). Tenecteplase is dosed according to body weight and given by intravenous bolus injection.

Reteplase is a deletion variant of t-PA that lacks both fibrin-binding domains and oligosaccharide side chains (manufactured in prokaryotic *E. coli).* It is eliminated more slowly than alteplase. Whereas alteplase is given by infusion, reteplase can be administered in two bolus injections spaced 30 minutes apart.

A further direct-acting plasmin analogue should be mentioned: **ocriplasmin** is injected into the eye to disrupt harmful protein bridges between the vitreous and retina (vitreomacular traction), which may occur in the elderly.

► **Plasmin inhibitors.** *Tranexamic acid* and *p-aminomethylbenzoic acid* (PAMBA) are plasmin inhibitors that can be useful in bleeding complications. They exert an inhibitory effect by occupying the fibrin binding site of plasminogen or plasmin.

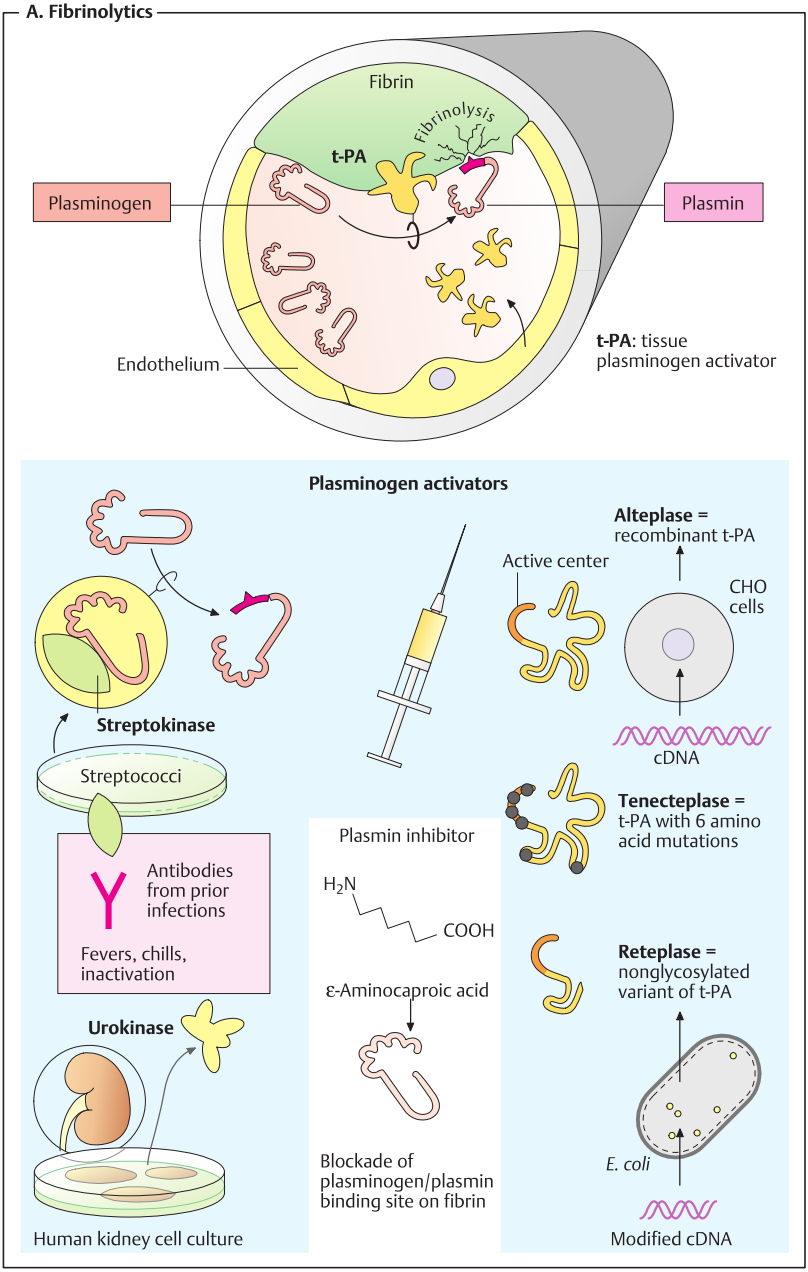

A. Fibrinolytics
Fibrin
Fibrinolysis
t-PA
Plasminogen
Plasmin
Endothelium
t-PA: tissue plasminogen activator
Plasminogen activators
Alteplase = recombinant t-PA
Active center
CHO cells
cDNA
Streptokinase
Streptococci
Antibodies from prior infections
Fevers, chills, inactivation
Tenecteplase = t-PA with 6 amino acid mutations
Plasmin inhibitor
H2N
COOH
ε-Aminocaproic acid
Reteplase = nonglycosylated variant of t-PA
Urokinase
Blockade of plasminogen/plasmin binding site on fibrin
E. coli
Human kidney cell culture
Modified cDNA

Fig. 20.4

Inhibitors of Platelet Aggregation

Platelets can aggregate when a vessel wall is injured or endothelial function is impaired (e.g., because of hypertension, raised plasma LDL levels, untreated diabetes mellitus, smoking). Interaction with von Willebrand factor and collagen causes platelets to adhere to the vessel wall and become activated. Activation induces a change in platelet shape and triggers secretion of substances stored in intracellular granules (e.g., ADP, serotonin). In addition, cyclooxygenase (COX-1) is stimulated so that thromboxane A_2 is produced from arachidonic acid. Released ADP and thromboxane A_2 activate G-protein-coupled receptors ($P2Y_{12}$ and TP receptors), which ultimately produce a change in the conformation of glycoprotein GP IIb/IIIa in the platelet membrane. The glycoprotein then has an affinity for fibrinogen and can induce the platelets to become cross-linked. A thrombus forms over an endothelial defect, which can impede blood flow or even occlude the vessel (e.g., in myocardial infarction or stroke).

The propensity of platelets to aggregate can be inhibited by various pharmacological interventions (▶ Fig. 20.5**A**).

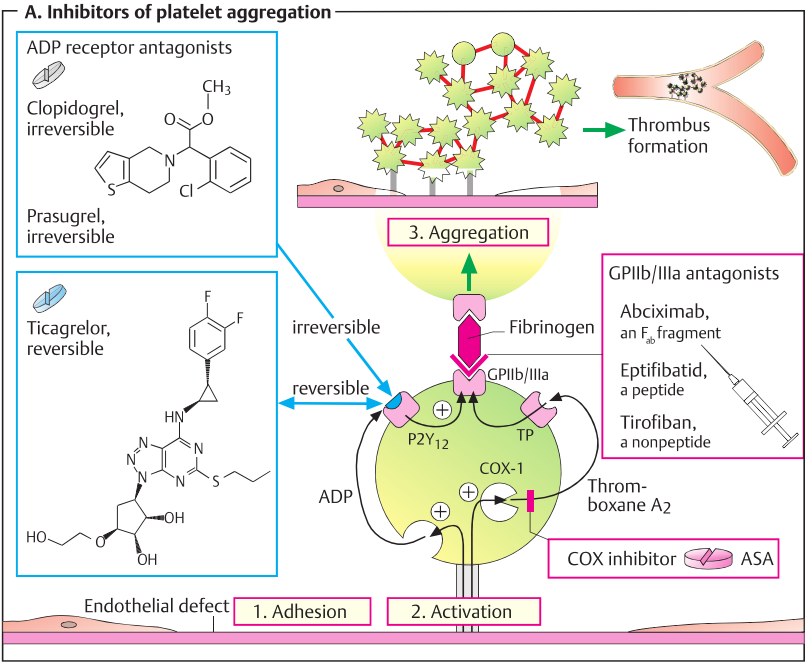
Acetylsalicylic acid (**ASA**) prevents COX-1-mediated synthesis of thromboxane. Low daily doses (75–100 mg) may be sufficient. Indications include prophylaxis of re-infarction after myocardial infarction and prevention of stroke. Despite the low dosage, adverse effects such as gastric mucosal damage or provocation of asthma attacks cannot be ruled out.

Available alternatives to ASA are the **ADP receptor antagonists**, which inhibit ADP-mediated platelet aggregation. Clopidrogel and the newer prasugrel block $P2Y_{12}$ ADP receptors irreversibly. Consequently, ADP-mediated platelet aggregation is inhibited for the duration of the platelet life cycle (~7–10 days). These substances are inactive precursors that are converted by hepatic cytochrome P450 to an active metabolite that binds covalently to the $P2Y_{12}$ receptor (▶ Fig. 20.5**B**). A large part of a clopidogrel dose is inactivated by esterases and its bioavailability can be influenced by genetic CYP polymorphisms. **Ticagrelor** is a reversible, competitive $P2Y_{12}$ antagonist that acts immediately and does not require activation in the liver. **Cangrelor** is a reversible $P2Y_{12}$ inhibitor which can be administered intravenously. ADP receptor antagonists are used to prevent stent thrombosis and reinfarction in patients with acute coronary syndromes (p. 328).

▶ **Antagonists at the integrin glycoprotein IIb/IIIa.** Available agents are suitable only for parenteral administration and, in clinical settings, are used in percutaneous coronary balloon distension or in unstable angina pectoris. They block the fibrinogen cross-linking protein and thus decrease fibrinogen-mediated meshing of platelets independently of the precipitating cause. *Abciximab* is a chimeric Fab-antibody fragment directed against GPIIb/IIIa protein. *Tirofiban* and *eptifibatide* act as competitive antagonists at the fibrinogen binding site. Because abciximab adheres to GPIIb/IIIa for a long time, days are required after injection of the drug before platelet aggregation again becomes possible. The effects of eptifibatide and tirofiban dissipate within a few hours. Because GPIIb/IIIa antagonists inhibit the common final pathway in platelet activation, they pose a risk of bleeding during treatment.

Presystemic Effect of ASA

The inhibition of platelet aggregation by ASA results from acetylation and blockade of platelet COX-1 (▶ Fig. 20.5**B**). The specificity of this reaction is achieved in the following manner: irreversible acetylation of the enzyme already occurs in the blood of the splanchnic region, that is, before the liver is reached. Since ASA is subject to extensive presystemic deacetylation, cyclooxygenases located posthepatically (e.g., in endothelial cells) are hardly affected. Confinement of COX-1 inhibition to platelets is further accentuated because enzyme can be re-synthesized in normal cells having a nucleus but not in the nonnucleated platelets.


A. Inhibitors of platelet aggregation
ADP receptor antagonists
Clopidogrel, irreversible
Prasugrel, irreversible
Ticagrelor, reversible
Thrombus formation
3. Aggregation
irreversible
reversible
Fibrinogen
GPIIb/IIIa
GPIIb/IIIa antagonists
Abciximab, an F_{ab} fragment
Eptifibatid, a peptide
Tirofiban, a nonpeptide
P2Y12
TP
COX-1
ADP
Throm-boxane A2
COX inhibitor
ASA
Endothelial defect
1. Adhesion
2. Activation

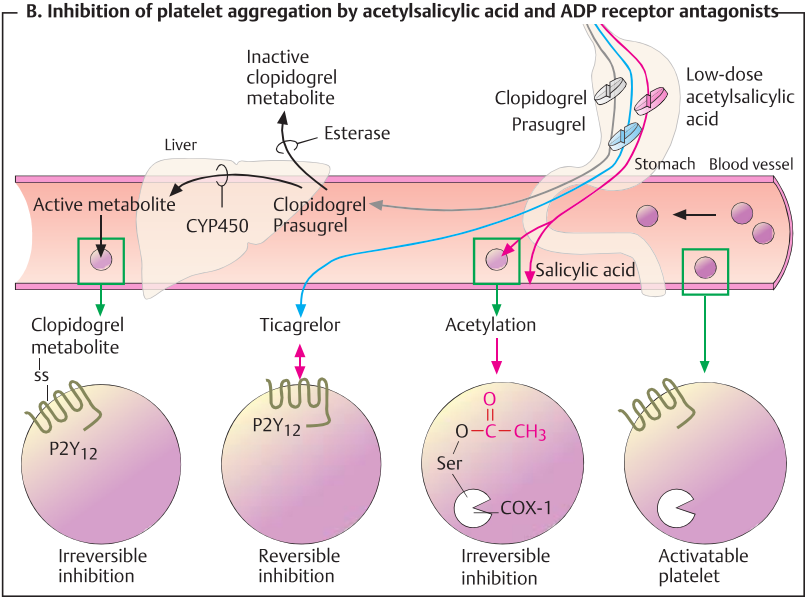

B. Inhibition of platelet aggregation by acetylsalicylic acid and ADP receptor antagonists
Inactive clopidogrel metabolite
Esterase
Liver
Clopidogrel
Prasugrel
Low-dose acetylsalicylic acid
Stomach
Blood vessel
Active metabolite
CYP450
Clopidogrel
Prasugrel
Salicylic acid
Clopidogrel metabolite
ss
Ticagrelor
Acetylation
P2Y12
P2Y12
O
O–C–CH3
Ser
COX-1
Irreversible inhibition
Reversible inhibition
Irreversible inhibition
Activatable platelet

Fig. 20.5

Plasma Volume Expanders

Major blood loss entails the danger of life-threatening circulatory failure, i.e., hypovolemic shock. The immediate threat results not so much from the loss of erythrocytes, i.e., oxygen carriers, as from the reduction in volume of circulating blood.

To eliminate the threat of shock, replenishment of the circulation is essential. With moderate loss of blood, administration of a plasma volume expander may be sufficient. Blood plasma consists basically of water, electrolytes, and plasma proteins. However, a plasma substitute need not contain **plasma proteins**. These can be suitably **replaced** with **macromolecules** ("colloids") that, like plasma proteins, (1) *do not readily leave the circulation and are poorly filterable in the renal glomerulus;* and (2) bind water along with its solutes owing to their *colloid osmotic properties.* **Hydroxyethyl starch** and cross-linked **gelatin** fragments are now used to correct volume losses and are well tolerated.

Hydroxyethyl starch is a branched polysaccharide. Its glucose molecules have a hydroxyethyl group in the 2-position. It comes as infusion solutions with different average molecular weights of 130 000 and 200 000 daltons (Da). In the blood, the molecules are slowly broken down into smaller fragments that can be eliminated by the kidneys. A particular adverse effect during prolonged use is pruritus, which is difficult to treat and may last for months.

Gelatin polymers are produced by partial degradation of gelatin molecules, which are then cross-linked by succinate bridges. These polymers have an average molecular weight of 35 000 Da and have an elimination half-life of about 4 hours. They occasionally cause an anaphylactic reaction.

In practice, these colloid solutions contain electrolytes plus the macromolecules in different concentrations. This is usually isotonic sodium chloride, but other ions (K^+, lactate) or glucose may be present. The choice of preparation should be guided by the condition of the hypovolemic patient.

Acute volume depletion can also be improved by infusion of plasma proteins in the form of human albumin and human serum preparations. **Freeze-dried plasma** products have an unrestricted shelf-life and are intended for special situations such as protein deficiency states.

When blood loss is so severe that the oxygen supply to the tissues is insufficient because of the loss of erythrocytes along with the hypovolemic shock, **blood transfusion** is essential.

Appendix: Stimulation of Blood Cell Formation

It should be mentioned here that pharmacological stimulation of endogenous blood cell formation is possible in addition to replacement of these cells by transfusion. The stimulator proteins can be produced by genetic engineering methods.

Erythropoietin is a glycoprotein consisting of 165 amino acids, which is normally synthesized in the kidneys. The genetically engineered analogues **epoetin alfa, beta, theta**, and **zeta** differ only in the structure of the sugar residues. By contrast, **darbepoetin alfa** has been altered so that it contains more glycosylation sites and elimination is therefore slower. In the case of **methoxy PEG-epoetin beta** a polyethylene glycol (PEG) chain provides slowed elimination.

Thrombopoietin is a glycoprotein consisting of 332 amino acids produced by different types of cells. **Romiplostim** is a fusion protein consisting of an antibody Fc fragment and essential thrombopoietin residues. A small molecule also suffices to activate the receptor, however,**eltrombopag** is not a protein and is suitable for oral administration.

Granulocyte colony-stimulating factor (G-CSF) is a glycoprotein consisting of 175 amino acids. "G-CSF-mimetics" include filgrastim (not glycosylated), PEG-filgrastim, its pegylated form, and glycosylated lenograstim.

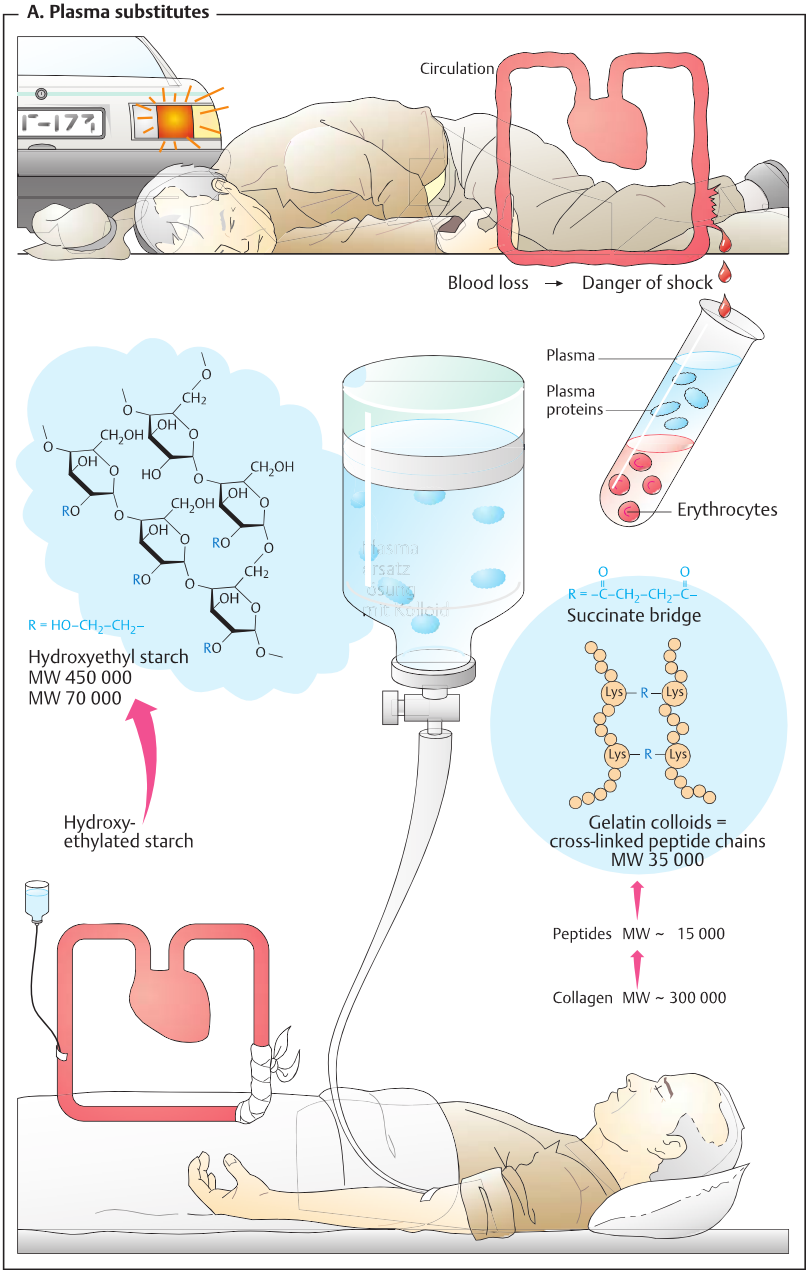

A. Plasma substitutes
Circulation
Blood loss → Danger of shock
Plasma
Plasma proteins
Erythrocytes
R = HO–CH2–CH2–
Hydroxyethyl starch
MW 450 000
MW 70 000
Hydroxy-
ethylated starch
R = –C–CH2–CH2–C–
Succinate bridge
Gelatin colloids =
cross-linked peptide chains
MW 35 000
Peptides MW ~ 15 000
Collagen MW ~ 300 000

Fig. 21.1

Lipid-lowering Agents

Triglycerides and cholesterol are essential constituents of the organism. Among other things, triglycerides represent a form of energy store and cholesterol is a basic building block of biological membranes. Both lipids are water insoluble and require appropriate "packaging" for transport in the aqueous media of lymph and blood. To this end, small amounts of lipid are coated with a layer of phospholipids, embedded in which are additional proteins—the apolipoproteins (▶ Fig. 22.1A). Four forms are distinguished according to the amount and composition of the stored lipids as well as the type of apolipoprotein.

▶ **Lipoprotein metabolism.** Enterocytes release absorbed lipids in the form of triglyceride-rich chylomicrons. Bypassing the liver, these enter the circulation mainly via the lymph and are hydrolyzed by extrahepatic endothelial lipoprotein lipases to liberate fatty acids. The remnant particles move on into liver cells and supply these with cholesterol of dietary origin.

The liver meets the larger part (60%) of its requirement for cholesterol by de novo synthesis from acetylcoenzyme A. Synthesis rate is regulated at the step leading from hydroxymethylglutaryl-CoA (HMG-CoA) to mevalonic acid (▶ Fig. 22.2A), with HMG-CoA reductase as the rate-limiting enzyme.

The liver requires cholesterol for synthesizing VLDL particles and bile acids. Triglyceride-rich VLDL particles are released into the blood and, like the chylomicrons, supply other tissues with fatty acids. Left behind are LDL particles that either return into the liver or supply extrahepatic tissues with cholesterol.

LDL particles carry the apolipoprotein B-100, by which they are bound to receptors that mediate uptake of LDL into the cells, including the hepatocytes (receptor-mediated endocytosis, p. 42).

HDL particles are able to transfer cholesterol from tissue cells to LDL particles. In this way, cholesterol is transported from tissues to the liver.

Hyperlipoproteinemias can be caused genetically (primary hyperlipoproteinemia) or can occur in obesity and metabolic disorders (secondary hyperlipoproteinemia). Elevated LDL-cholesterol serum concentrations are associated with an increased risk of atherosclerosis, especially when there is a concomitant decline in HDL concentration (increase in LDL : HDL ratio).

▶ **Treatment.** Various drugs are available that have different mechanisms of action and effects on LDL (cholesterol) and VLDL (triglycerides). Their use is indicated in the therapy of primary hyperlipoproteinemias. In secondary hyperlipoproteinemias, the immediate goal should be to lower lipoprotein levels by dietary restriction, treatment of the primary disease, or both. In terms of therapeutic benefit, the "statins" are the outstanding group.

Table 22.1 Lipoproteins

	Origin	Density	Mean time in blood plasma (h)	Diameter (nm)
Chylomicron	Gut epithelium	> 1.006	0.2	500 or more
VLDL particle	Liver	0.95–1.006	3	100–200
LDL particle	(Blood)	1.006–1.063	50	25
HDL particle	Liver	1.063–1.210	–	5–10

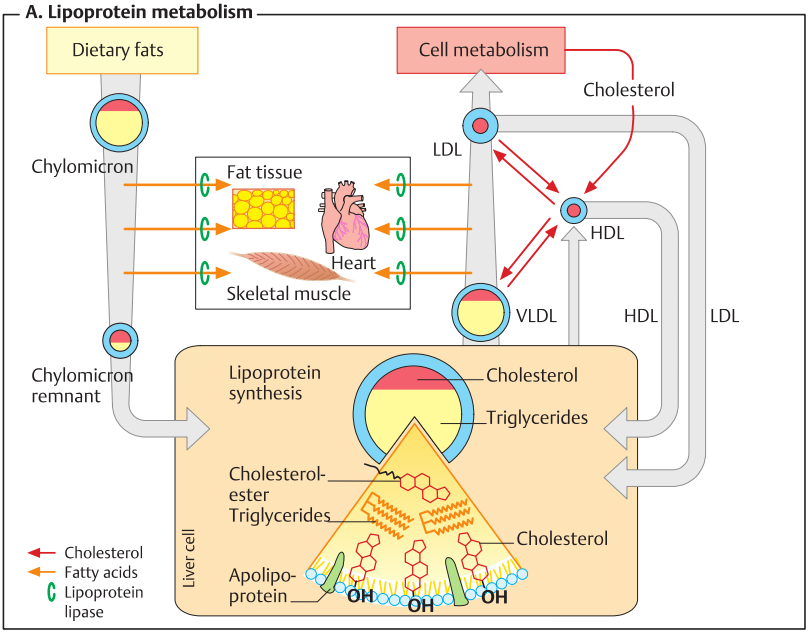

A. Lipoprotein metabolism
Dietary fats
Cell metabolism
Cholesterol
Chylomicron
LDL
Fat tissue
Heart
Skeletal muscle
HDL
VLDL
HDL
LDL
Chylomicron remnant
Lipoprotein synthesis
Cholesterol
Triglycerides
Cholesterol-ester
Triglycerides
Cholesterol
Apolipo-protein
OH
OH
OH
Liver cell
Cholesterol
Fatty acids
Lipoprotein lipase
B. Cholesterol metabolism in liver cell and cholesterol-lowering drugs
Cholestyramine
Gut: binding and excretion of bile acids (BA)
→ Liver: BA synthesis↑
→ Cholesterol consumption↑
Bile acids
Lipoproteins
Cholesterol store
Liver cell
LDL
Ezetimibe
F
HO
N
O
CH2
CH2
HO—CH
F
Gut: cholesterol absorption↓
Synthesis
HMG-CoA-Reductase inhibitors

Fig. 22.1

► **Drugs.** *Cholestyramine* and *colestipol* are exchange resins that can bind bile acids in the gut lumen, thus removing them from enterohepatic circulation. This means that cholesterol is used to produce further bile acids. The dosage is quite high, in the gram range, and can cause troublesome gastrointestinal side effects.

Ezetimibe inhibits cholesterol absorption from the gut by blocking a sterol transporter in the brush border of enterocytes. The daily dosage is only 10 mg and this reduces the blood cholesterol level by about 20%. There is still no evidence that ezetemibe is of benefit in atherosclerotic disorders.

The **statins** *lovastatin* and *fluvastatin* inhibit HMG-CoA reductase. They contain a molecular moiety that chemically resembles the physiological substrate of the enzyme (► Fig. 22.2**A**). Lovastatin is a lactone that is rapidly absorbed by the enteral route, subjected to extensive first-pass extraction in the liver, and there hydrolyzed to active metabolites. Fluvastatin represents the active form and, as an acid, is actively transported by a specific anion carrier (OATP) that moves bile acids from blood into liver and also mediates the selective uptake of the mycotoxin amanitine (► Fig. 22.2**A**). Normally viewed as presystemic elimination, efficient hepatic extraction serves to confine the action of statins to the liver. Despite the inhibition of HMG-CoA reductase, hepatic cholesterol content does not fall because hepatocytes compensate any drop in cholesterol levels by increasing the synthesis of LDL receptor protein (along with the reductase). Since, in the presence of statins, the newly-formed reductase is inhibited as well, the hepatocyte must meet its cholesterol demand entirely by uptake of LDL from the blood (► Fig. 22.2**B**). Accordingly, the concentration of circulating LDL falls. As LDL remains in blood for a shorter time, the likelihood of LDL being oxidized to its proatherogenic degradation product decreases pari passu.

Other statins include *simvastatin* (also a lactone prodrug), *pravastatin, atorvastatin, rosuvastatin* and *pitavastatin* (active form with open ring).

The statins are the most important therapeutics for lowering cholesterol levels. Their notable cardiovascular protective effect, however, appears to involve additional actions in addition to LDL reduction.

The combination of a statin with an inhibitor of cholesterol absorption (e.g., *ezetimibe)* can lower LDL levels even further.

A rare but dangerous adverse effect of statins is damage to skeletal muscle (rhabdomyolysis). This risk is increased by combined use of fibric acid agents (see below). Cerivastatin has proved particularly toxic. Besides muscle damage associated with myoglobinuria and renal failure, severe hepatotoxicity has also been noted, prompting withdrawal of the drug.

PCSK9 (Proprotein convertase subtilisin/kexin type 9) binds to LDL receptors in the plasma membrane of hepatocytes and facilitates LDL receptor endocytosis and lysosomal degradation. When PCSK9 is blocked, more LDL receptors recycle to the cell surface to remove LDL particles containing cholesterol from the blood. The monoclonal antibodies inhibiting PCSK9, ***alirocumab*** and ***evolocumab*** were recently approved for lowering LDL cholesterol when statins were not tolerated or not effective.

Nicotinic acid preparations have not proved effective and their use has been abandoned.

Clofibrate and derivatives *(bezafibrate, fenofibrate, and gemfibrozil)* lower concentrations of VLDL (triglycerides) along with LDL (cholesterol). They may cause damage to liver and skeletal muscle (myalgia, myopathy, rhabdomyolysis with myoglobinemia and renal failure). The mechanism of action of fibrates is not completely understood. They bind to a peroxisome proliferator-activated receptor (PPARα) and thereby influence genes regulating lipid metabolism.

Lomitapide can be used in combination with other treatments in the very rare congenital homozygous familial hypercholesterolemia. It reduces the blood concentrations of chylomicrons, VLDL, and LDL by intracellular inhibition of lipid transport processes in the intestinal epithelium and liver.

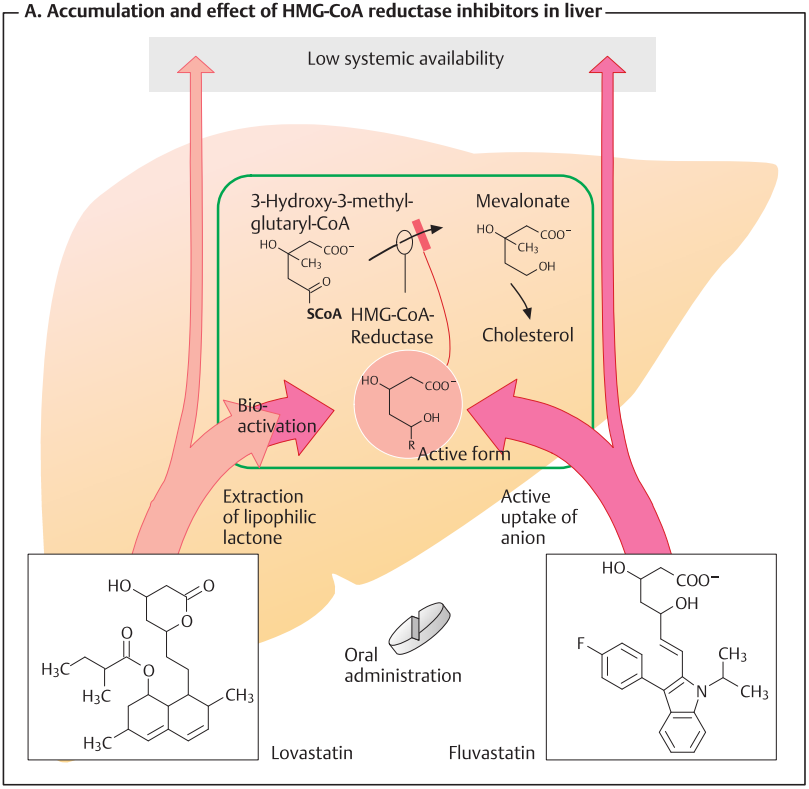

A. Accumulation and effect of HMG-CoA reductase inhibitors in liver
Low systemic availability
3-Hydroxy-3-methyl-glutaryl-CoA
Mevalonate
SCoA
HMG-CoA-Reductase
Cholesterol
Bio-activation
Active form
Extraction of lipophilic lactone
Active uptake of anion
Oral administration
Lovastatin
Fluvastatin
B. Regulation of HMG-CoA reductase and LDL receptors by cellular cholesterol concentration
Inhibition of HMG-CoA reductase
LDL receptor
HMG-CoA reductase
Gene expression
Gene expression
Cholesterol
LDL in blood
Increased receptor-mediated uptake of LDL

Fig. 22.2

Diuretics—Overview

Diuretics (saluretics) elicit increased production of urine (diuresis). In the strict sense, the term is applied to drugs with a direct renal action. The predominant action of such agents is to augment urine excretion by inhibiting the reabsorption of NaCl and water.

The most important **indications** for diuretics are the following.

Mobilization of edema (▶ Fig. 23.1**A**). In edema there is swelling of tissues owing to accumulation of fluid, chiefly in the extracellular (interstitial) space. When a diuretic is given, increased renal excretion of Na^+ and H_2O causes a reduction in plasma volume with hemoconcentration. As a result, plasma protein concentration rises along with oncotic pressure. As the latter operates to attract water, fluid will shift from the interstitium into the capillary bed. The fluid content of tissues thus falls and the edema recedes. The decrease in plasma volume and interstitial volume means a diminution of the extracellular fluid volume (EFV). Depending on the condition, use is made of thiazides, loop diuretics, aldosterone antagonists, and osmotic diuretics.

Antihypertensive therapy. Diuretics have been used as drugs of first choice for lowering elevated blood pressure (p. 322). Even at low dosage, they decrease peripheral resistance (without significantly reducing EFV) and thereby normalize blood pressure.

Therapy of congestive heart failure (p. 330): By lowering peripheral resistance, diuretics aid the heart in ejecting blood (reduction in afterload); cardiac output and exercise tolerance are increased. Owing to the increased excretion of fluid, EFV and venous return decrease (reduction in preload). Symptoms of venous congestion, such as ankle edema and hepatic enlargement, subside. The drugs principally used are thiazides (possibly combined with K^+-sparing diuretics) and loop diuretics.

Prophylaxis of renal failure. In circulatory failure (shock), e.g., secondary to massive hemorrhage, renal production of urine may cease (anuria). By means of diuretics, an attempt is made to maintain urinary flow. Use of either osmotic or loop diuretics is indicated.

Massive use of diuretics entails a hazard of **adverse effects** (▶ Fig. 23.1**A**):

1. The decrease in blood volume can lead to hypotension and *collapse*.
2. Blood viscosity rises owing to the increase in erythrocyte and thrombocyte concentrations, bringing an increased risk of intravascular coagulation or *thrombosis*.

When depletion of NaCl and water (EFV reduction) occurs as a result of diuretic therapy, the body can initiate **counter-regulatory responses** (▶ Fig. 23.1**B**), namely, activation of the renin–angiotensin–aldosterone system (p. 142). Because of the diminished blood volume, renal blood flow is jeopardized. This leads to release from the kidneys of the hormone renin, which enzymatically catalyzes the formation of angiotensin I. Angiotensin I is converted to angiotensin II by the action of "angiotensin-converting enzyme" (ACE). Angiotensin II stimulates release of aldosterone. The mineralocorticoid promotes renal reabsorption of NaCl and water and thus counteracts the effect of diuretics. ACE inhibitors (p. 142) and angiotensin II antagonists augment the effectiveness of diuretics by preventing this counter-regulatory response.

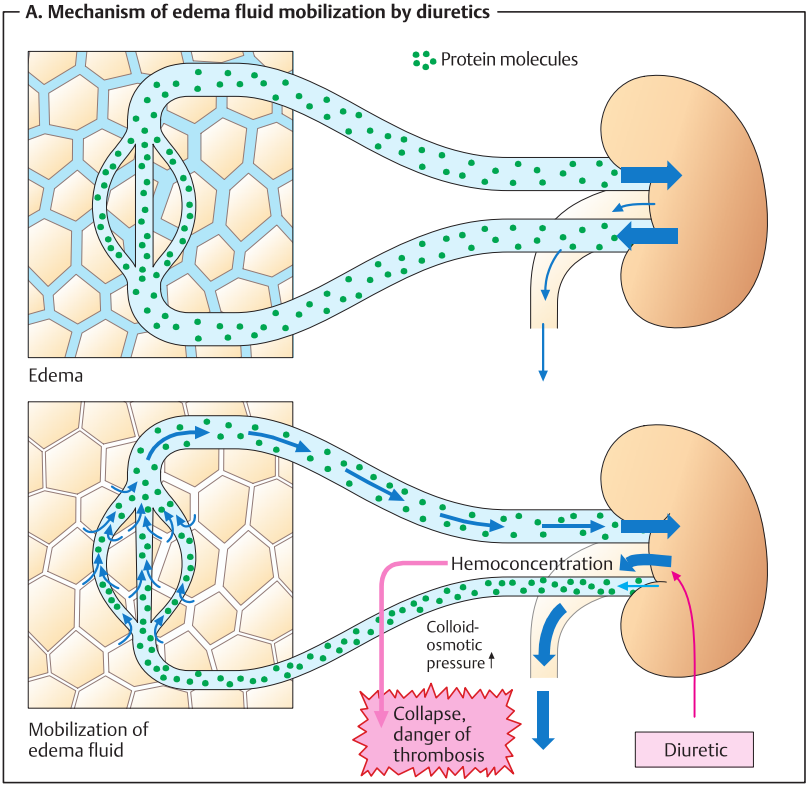

A. Mechanism of edema fluid mobilization by diuretics
Protein molecules
Edema
Hemoconcentration
Colloid-osmotic pressure ↑
Collapse, danger of thrombosis
Diuretic
Mobilization of edema fluid
B. Possible counter-regulatory responses during long-term diuretic therapy
Salt and fluid retention
EFV:
Na+, Cl-,
H2O
Diuretic
Diuretic
Angiotensinogen
Renin
Angiotensin I
ACE
Angiotensin II
Aldosterone

Fig. 23.1

NaCl Reabsorption in the Kidney

The smallest functional unit of the kidney is the **nephron** (▶ Fig. 23.2**A**). In the glomerular capillary loops, ultrafiltration of plasma fluid into Bowman's capsule yields primary urine. In the proximal tubules, ~70% of the ultrafiltrate is retrieved by iso-osmotic reabsorption of NaCl and water. Downstream, in the thick portion of the ascending limb of the loop of Henle, NaCl is absorbed unaccompanied by water. The differing properties of the limbs of the loop of Henle, together with the parallel arrangement of vasa recta, are the prerequisites for the **hairpin countercurrent mechanism** that allows build-up of a very high NaCl concentration in the renal medulla. NaCl is again reabsorbed in the distal convoluted tubules, the connecting segment, and the collecting ducts, accompanied by a compensatory secretion of K^+ in the (cortical) collecting tubules. In the connecting tubules and collecting ducts, vasopressin (antidiuretic hormone, ADH) increases the epithelial permeability for water by insertion of aquaporin molecules into the luminal plasmalemma. The driving force for the passage of water comes from the hyperosmolar milieu of the renal medulla. In this manner, water is retained in the body, and concentrated urine can leave the kidney. The efficient mechanisms of reabsorption permit the production of ~1 liter/day of final urine from 150–180 liters/day of primary urine.

Na^+ transport through the tubular cells basically occurs in similar fashion in all segments of the nephron. The intracellular concentration of Na^+ is significantly below that in primary urine because the Na^+/K^+-ATPase of the basolateral membrane continuously pumps Na^+ from the cell into the interstitium. Along the resulting luminal–intracellular concentration gradient, movement of sodium ions across the membrane proceeds by a carrier mechanism. All diuretics inhibit Na^+ reabsorption. This effect is based on two mechanisms: either the inward movement is diminished or the outward transport impaired.

Aquaporins (AQP)

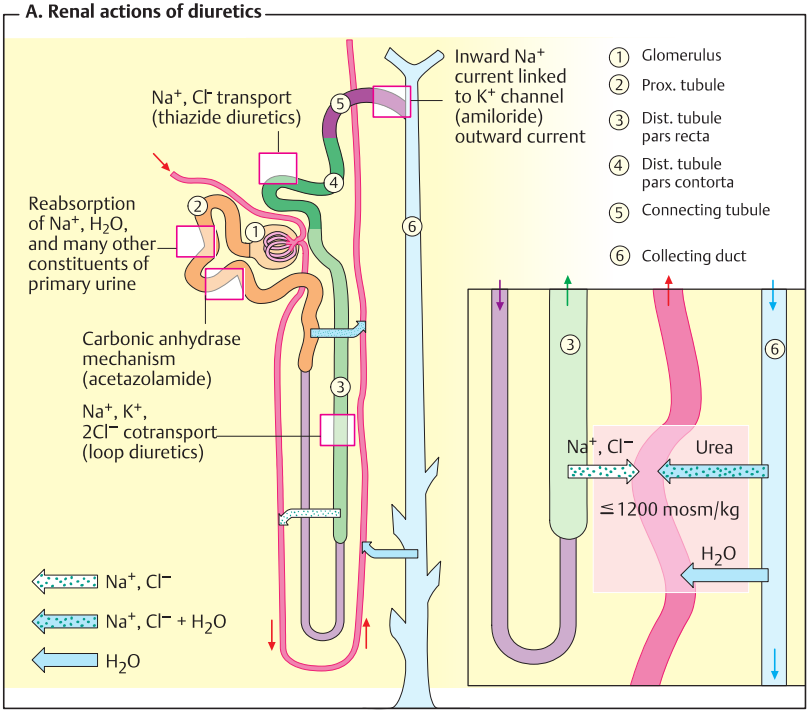
By virtue of their structure, cell membranes are water-impermeable. Therefore, special pores are built into the membrane to allow permeation of water. These consist of proteins called **aquaporins** that, of necessity, occur widely and with many variations in both the plant and animal kingdoms. In the human kidney, the following types exist:

- AQP-1 localized in the proximal tubule and the descending limb of the loop of Henle.
- AQP-2 localized in the connecting tubules and collecting ducts; its density in the luminal plasmalemma is regulated by vasopressin.
- AQP-3 and AQP-4 present in the basolateral membrane region to allow passage of water into the interstitium (▶ Fig. 23.2**B**).

The renal action of **aldosterone** may be described here. This adrenocortical hormone stimulates synthesis of Na^+/K^+-ATPases and of Na^+ and K^+ channels. The result is increased reabsorption of water and Na^+. Accordingly, an antagonist such as spironolactone or eplerenone will have a diuretic effect.

Osmotic Diuretics

These include *mannitol* and *sorbitol* which act mainly in the proximal tubules to prevent reabsorption of water. These polyhydric alcohols cannot be absorbed and therefore bind a corresponding volume of water. Since body cells lack transport mechanisms for these substances they also cannot be absorbed through the intestinal epithelium and thus need to be given by intravenous infusion. The result of osmotic diuresis is a large volume of dilute urine, as in decompensated diabetes mellitus. To achieve effective osmotic diuresis, an intravenous infusion of 0.5–2 liters of 10% mannitol may be needed. This is a severe load on the heart and circulation (pulmonary edema), and may result in hyperinfusion syndrome.


A. Renal actions of diuretics
Na+, Cl− transport (thiazide diuretics)
Inward Na+ current linked to K+ channel (amiloride) outward current
Reabsorption of Na+, H2O, and many other constituents of primary urine
Carbonic anhydrase mechanism (acetazolamide)
Na+, K+, 2Cl− cotransport (loop diuretics)
1 Glomerulus
2 Prox. tubule
3 Dist. tubule pars recta
4 Dist. tubule pars contorta
5 Connecting tubule
6 Collecting duct
Na+, Cl−
Urea
≤1200 mosm/kg
H2O
Na+, Cl−
Na+, Cl− + H2O
H2O

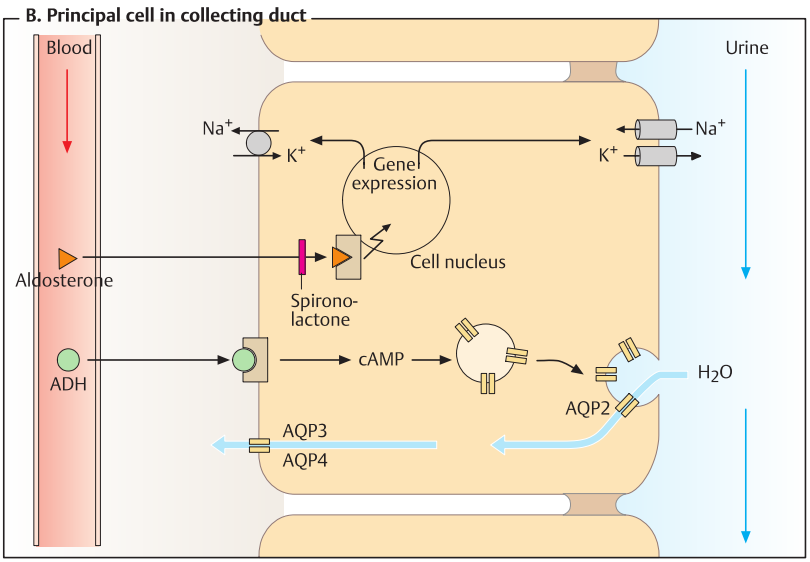

B. Principal cell in collecting duct
Blood
Urine
Na+
K+
Gene expression
Cell nucleus
Aldosterone
Spirono-lactone
ADH
cAMP
H2O
AQP2
AQP3
AQP4

Fig. 23.2

Diuretics of the Sulfonamide Type

These drugs contain the sulfonamide group-SO_2NH_2 and are suitable for oral administration. In addition to being filtered at the glomerulus, they are subject to tubular secretion. Their concentration in urine is higher than in blood. They act on the tubule cells from the luminal side. Loop diuretics have the highest efficacy. Thiazides are most frequently used. The carbonic anhydrase inhibitors no longer serve as diuretics but have important other therapeutic uses (see p. 346); accordingly, their mode of action is considered here.

Acetazolamide is a **carbonic anhydrase (CAH) inhibitor** that acts predominantly in the proximal convoluted tubules. Its mechanism of action can be summarized as follows. Reabsorption of Na^+ is decreased because fewer H^+ ions are available for the Na^+/H^+ antiporter. As a result, excretion of Na^+ and H_2O increases. CAH accelerates attainment of equilibrium of CO_2 hydration/dehydration reactions:

$$H^+ + HCO_3^- \rightleftarrows H_2CO_3 \rightleftarrows H_2O + CO_2 \qquad (23.1)$$

Cytoplasmic enzyme is used in tubule cells to generate H^+ (reaction 1), which is secreted into the tubular fluid in exchange for Na^+. There, H^+ captures HCO_3^-. CAH localized in the luminal membrane catalyzes reaction 2 (dehydration) to yield again H_2O and CO_2, which can easily permeate through the cell membrane. In the tubule cell, H^+ and HCO_3^- are regenerated. When the enzyme is inhibited, these reactions occur too slowly, so that less Na^+, HCO_3^-, and water are reabsorbed from the fast-flowing tubular fluid. Loss of HCO_3^- leads to acidosis. The diuretic effectiveness of CAH inhibitors decreases with prolonged use. CAH is also involved in the production of ocular aqueous humor. Present indications for drugs in this class include: acute glaucoma, acute mountain sickness, and epilepsy.

Dorzolamide can be applied topically to the eye to lower intraocular pressure in glaucoma (p. 346).

Loop diuretics include *furosemide* (frusemide), *piretanide, torasemide,* and others. After oral administration of furosemide, a strong diuresis occurs within 1 hour but persists for only about 4 hours. The site of action of these agents is the thick ascending limb of the loop of Henle, where they inhibit $Na^+/K^+/2Cl^-$ cotransport. As a result, these electrolytes, together with water, are excreted in larger amounts. Excretion of Ca^{2+} and Mg^{2+} also increases. Special *adverse effects* include (reversible) hearing loss and enhanced sensitivity to nephrotoxic agents. *Indications:* pulmonary edema (added advantage of i.v. injection in left ventricular failure: immediate dilation of venous capacitance vessels → preload reduction); refractoriness to thiazide diuretics; e.g., in renal failure with creatinine clearance reduction (< 30 mL/min); prophylaxis of acute renal hypovolemic failure.

Thiazide diuretics (benzothiadiazines) include *hydrochlorothiazide, xipamide,* and *indapamide. Chlorthalidone* is a long-acting analogue. These drugs affect the distal convoluted tubules, where they inhibit Na^+/Cl^- cotransport in the luminal membrane of tubule cells. Thus, reabsorption of NaCl and water is inhibited. Renal excretion of Ca^{2+} decreases, that of Mg^{2+} increases. *Indications* are hypertension, congestive heart failure, and mobilization of edema. Frequently, they are combined with the K^+-sparing diuretics triamterene or amiloride (p. 180).

Unwanted effects of sulfonamide-type diuretics: (a) *hypokalemia* is a consequence of an increased secretion of K^+ in the connecting tubule and the collecting duct because more Na^+ becomes available for exchange against K^+; (b) *hyperglycemia;* (c) increase in serum urate levels *(hyperuricemia),* which may precipitate gout in predisposed patients as sulfonamide diuretics compete with urate for the tubular organic anion secretory system. Further unwanted effects are hypovolemia, hyponatremia, fall in plasma Mg^{2+} and Cl^-. Thiazides inhibit renal Ca^{2+} elimination, whereas loop diuretics promote this. Lipid levels may increase.

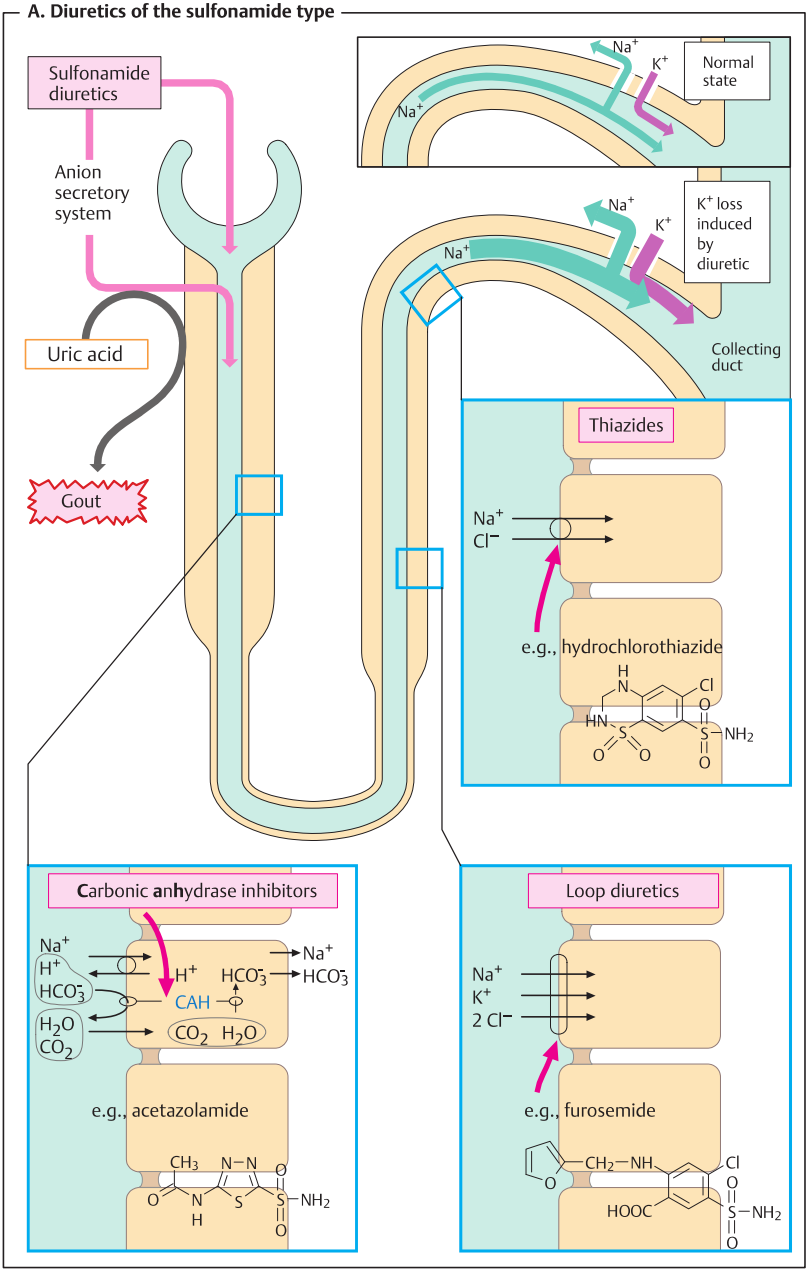

A. Diuretics of the sulfonamide type
Sulfonamide diuretics
Anion secretory system
Uric acid
Gout
Normal state
K+ loss induced by diuretic
Collecting duct
Thiazides
e.g., hydrochlorothiazide
Carbonic anhydrase inhibitors
CAH
e.g., acetazolamide
Loop diuretics
e.g., furosemide

Fig. 23.3

Potassium-sparing Diuretics

These agents act in the connecting tubules and the proximal part of the collecting ducts where Na^+ is reabsorbed and K^+ is secreted (▶ Fig. 23.4**A**). Their diuretic effectiveness is relatively minor. In contrast to sulfonamide diuretics (p. 178), there is no increase in K^+ secretion; rather, there is a risk of hyperkalemia. These drugs are suitable for oral administration.

a) *Triamterene* and *amiloride,* in addition to glomerular filtration, undergo secretion in the proximal tubule. They act on cortical collecting tubule cells from the luminal side. Both inhibit the entry of Na^+ into the cell, whereby K^+ secretion is diminished. They are mostly used in combination with thiazide diuretics, e.g., hydrochlorothiazide, because the opposing effects on K^+ excretion cancel each other, while the effects on secretion of NaCl and water complement each other.

b) *Aldosterone antagonists.* The mineralocorticoid aldosterone increases synthesis of Na^+ channel proteins and Na^+/K^+-ATPases in principal cells of the connecting tubules and the cortical collecting ducts, thereby promoting the reabsorption of Na^+ (Cl^- and H_2O follow), and simultaneously enhancing secretion of K^+. *Spironolactone,* as well as its *metabolite canrenone,* are antagonists at the aldosterone receptor and attenuate the effect of the hormone. The diuretic effect of spironolactone develops fully only with continuous administration for several days.

A disadvantage of spironolactone is its lack of specificity for the aldosterone receptor. It also binds to sex hormone receptors, which can lead to hormonal disorders such as gynecomastia and amenorrhea. *Eplerenone* is a recently developed aldosterone antagonist that binds specifically to the aldosterone receptor. This drug does not cause any hormonal side effects. The indications are edema due to hepatic cirrhosis and chronic heart failure. At low dosage, the aldosterone antagonists also have a beneficial effect on heart failure not associated with edema, and have been shown to prolong life.

Vasopressin and Derivatives

Vasopressin (antidiuretic hormone, ADH; arginine-vasopressin, AVP) (▶ Fig. 23.4**B**), a nonapeptide, is released from the posterior pituitary gland and promotes reabsorption of water in the kidney. This response is mediated by vasopressin receptors of the V_2 subtype. AVP enhances the permeability of connecting tubules and medullary collecting duct epithelium for H_2O (but not electrolytes) in the following manner: H_2O channel proteins (type 2 aquaporins) are stored in tubule cells within vesicles (▶ Fig. 23.2). When AVP binds to V_2 receptors, these vesicles fuse with the luminal cell membrane, allowing influx of H_2O along its osmotic gradient (the medullary zone is hyperosmolar). AVP thus causes urine volume to shrink from 15 liters/day at this point of the nephron to the final 1.5 liters/day. This aquaporin type can be reutilized after internalization into the cell. Nicotine augments and ethanol decreases release of AVP. At concentrations above those required for antidiuresis, AVP stimulates smooth musculature, including that of blood vessels (**"vasopressin"**). The latter response is mediated by V_1 receptors. Blood pressure rises; coronary vasoconstriction can precipitate angina pectoris.

Lypressin (8-L-lysine-vasopressin) acts like AVP. Other derivatives may display only one of the two actions.

▶ **Modulation of the V_2 receptor.** *Desmopressin* is used for the therapy of diabetes insipidus (AVP deficiency), primary nocturnal enuresis, and von Willebrand disease; it is given by injection or as a nasal spray.

Tolvaptan is a *V_2 antagonist* which may be used to block V_2 receptors when AVP levels are too high (p. 182). The molecule is modified to allow oral application of tolvaptan.

▶ **Modulation of the V_1 receptor.** The vasoconstrictor effect of *terlipressin* (or its active form lypressin) is utilized in life-threatening hemorrhage from esophageal varices. *Felypressin* is added to local anesthetics to act as vasoconstrictor (p. 206).

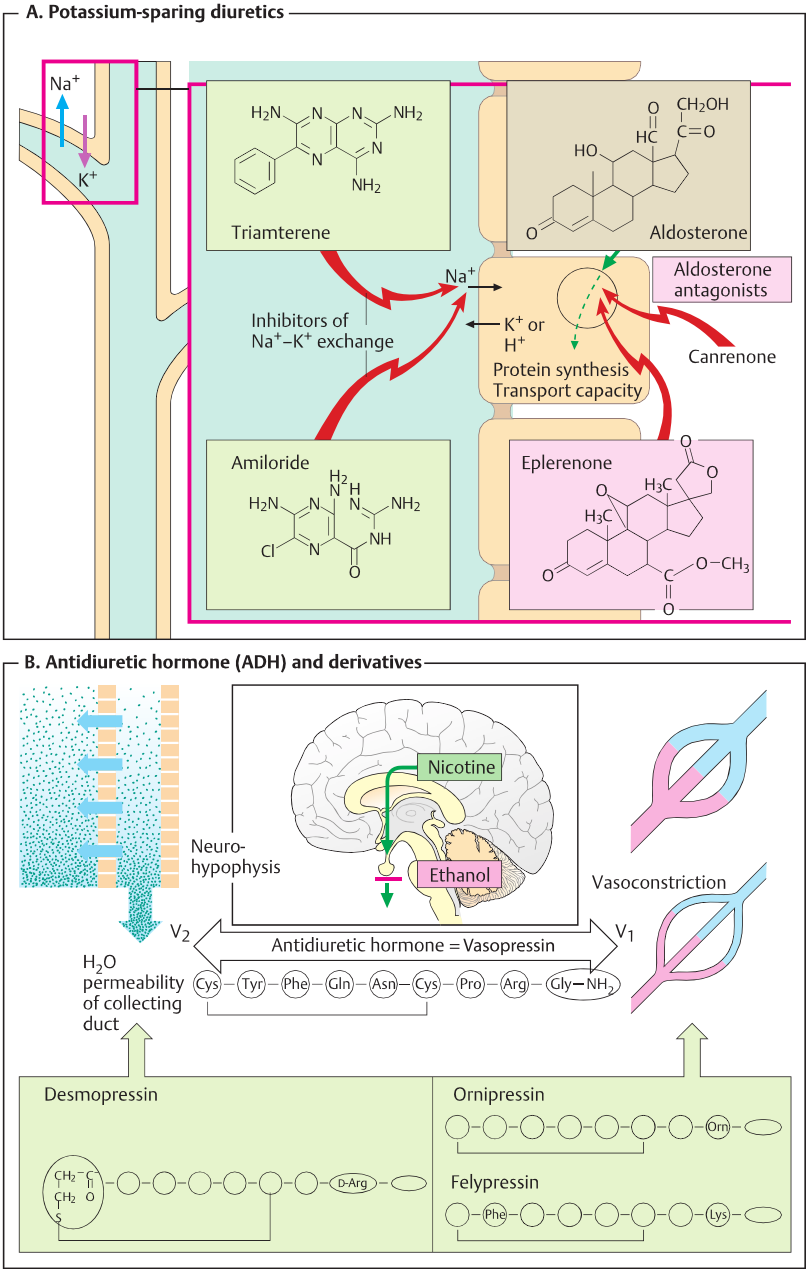

A. Potassium-sparing diuretics
Na+
K+
Triamterene
Aldosterone
Aldosterone antagonists
Inhibitors of Na+–K+ exchange
K+ or H+
Protein synthesis Transport capacity
Canrenone
Amiloride
Eplerenone
B. Antidiuretic hormone (ADH) and derivatives
Nicotine
Ethanol
Neuro-hypophysis
Vasoconstriction
V2
V1
Antidiuretic hormone = Vasopressin
H2O permeability of collecting duct
Cys Tyr Phe Gln Asn Cys Pro Arg Gly NH2
Desmopressin
D-Arg
Ornipressin
Orn
Felypressin
Phe
Lys

Fig. 23.4

Water and Electrolyte Disorders

There are large quantities of sodium and potassium in the body. The levels in the extracellular and intracellular spaces must be controlled precisely for the body to function normally.

Disorders of Na^+ Homeostasis

Na^+ and Cl^- bind water by osmotic force, thus determining the volume of the extracellular fluid (ECF). Blood volume depends on the ECF, and blood pressure in turn depends on blood volume. A change in the Na^+ and Cl^- content of the body results primarily in a change in the ECF. Conversely, the Na^+ and Cl^- concentration and osmolality (representing the number of particles per kg of solvent) of the ECF alter when there is a change in the body's water content. The ECF is regulated by the renin–angiotensin–aldosterone system (RAAS) in particular (p. 142), as aldosterone stimulates renal reabsorption of Na^+ and Cl^- and consequently H_2O. Osmolality is controlled by antidiuretic hormone (ADH, vasopressin, p. 180), which promotes renal reabsorption of water. ADH release from the posterior lobe of the pituitary is determined by ECF osmolality. However, a major reduction in circulating blood volume and arterial blood pressure also stimulate ADH release.

► **Hyponatremia (serum Na^+ <135 mmol/L).** Three situations can arise: (1) There is loss of fluid isotonic with the ECF, with a reduction of ECF (hypovolemia). If this can be compensated only by fluids with an inadequate Na^+ and Cl^- content, RAAS activation is insufficient and the ADH effect predominates. (2) Diseases associated with edema, when arterial pressure is reduced, which increases ADH secretion—the most common cause. (3) Excessive ADH secretion (e.g., Schwartz-Bartter syndrome, neuropsychiatric disorders, severe pain, some drugs) or excessive (parenteral) fluid intake. *Treatment:* eliminate the cause, if possible; otherwise, as shown in ► Fig. 24.1. One antagonist of the V_2 subtype is available, namely, tolvaptan.

► **Hypernatremia (serum Na^+ 150 mmol/L).** (1) *Water deficit.* Either water intake is too low (reduced sensation of thirst, e.g., in elderly persons or patients with a reduced level of consciousness) or *water excretion* is too high (ADH deficiency or renal ADH resistance, pituitary or nephrogenic diabetes insipidus). The latter can occur during treatment of bipolar disorder (p. 230) with lithium salts. The ECF is reduced in all these cases. (2) *Na^+ overload* not associated with a reduction of ECF, e.g., administration of parenteral penicillin G as the sodium salt.

► **Disorders of K^+ Homeostasis.** Over 95% of K^+ in the body is intracellular. It is able to leave the cells through ion channels according to its concentration gradient and is pumped back in by Na^+/K^+-ATPase. Changes in potassium metabolism must be taken very seriously because of the risk of cardiac dysfunction and arrhythmia.

► **Hypokalemia (serum K^+ <3.5 mmol/L).** Either oral intake is too low or, more importantly, K^+ is lost from the body, either through the kidneys (diuretics, amphotericin B, cardiac glycoside overdose) or from the gastrointestinal tract (cytostatic-induced vomiting, laxative abuse). *Treatment:* eliminate the cause, or K^+ replacement (caution: hyperkalemia if given parenterally).

► **Hyperkalemia (serum K^+ >5.5 mmol/L).** Renal elimination may be reduced (e.g., by potassium-sparing diuretics, RAAS inhibitors) or more K^+ passes into the ECF from the cellular compartment, e.g., with ion channel opening by suxamethonium (p. 192) or inhibition of cellular reabsorption by cardiac glycosides. Treatment: eliminate the cause, otherwise loop diuretics (to promote renal elimination), administration of insulin and glucose (to promote cellular K^+ uptake), dialysis.

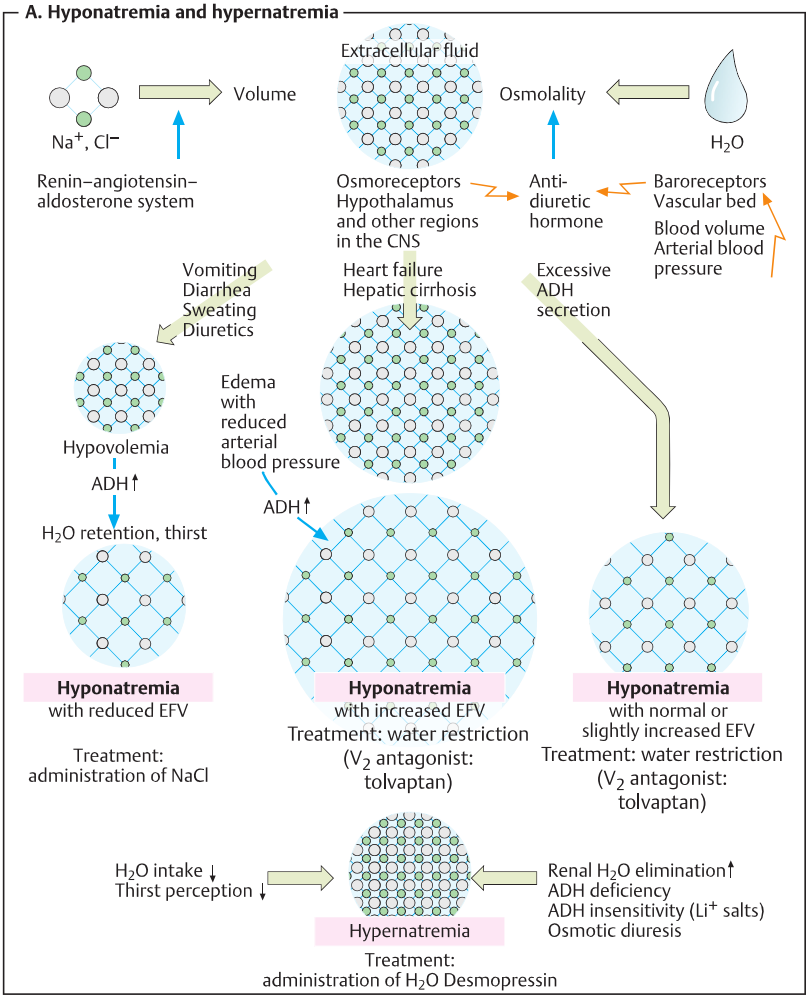

A. Hyponatremia and hypernatremia
Extracellular fluid
Volume
Osmolality
Na^+, Cl^-
H_2O
Renin–angiotensin–aldosterone system
Osmoreceptors Hypothalamus and other regions in the CNS
Anti-diuretic hormone
Baroreceptors Vascular bed
Blood volume Arterial blood pressure
Vomiting Diarrhea Sweating Diuretics
Heart failure Hepatic cirrhosis
Excessive ADH secretion
Hypovolemia
ADH↑
Edema with reduced arterial blood pressure
ADH↑
H_2O retention, thirst
Hyponatremia with reduced EFV
Treatment: administration of NaCl
Hyponatremia with increased EFV
Treatment: water restriction (V_2 antagonist: tolvaptan)
Hyponatremia with normal or slightly increased EFV
Treatment: water restriction (V_2 antagonist: tolvaptan)
H_2O intake↓ Thirst perception↓
Renal H_2O elimination↑ ADH deficiency ADH insensitivity (Li^+ salts) Osmotic diuresis
Hypernatremia
Treatment: administration of H_2O Desmopressin
B. Hypokalemia and hyperkalemia
Hypokalemia
Oral intake↓
K^+↓
Elimination↑
• Renal (diuretics, aldosterone, cortisol)
• Enteral (laxatives)
Treatment: K^+ replacement
Hyperkalemia
Digitalis intoxication
Suxa-methonium
K^+↑
Elimination↓
• K^+-sparing diuretics
• Inhibitors of the renin–angiotensin–aldosterone system
Treatment: loop diuretics, insulin/glucose, dialysis

Fig. 24.1

Therapy of Gastric and Duodenal Ulcers

Treatment of Hyperacidity

Under physiological conditions, acid–base concentrations are balanced on the surface of the gastric mucosa and in gastric juice. The pH in the mucus layer is roughly neutral, but there is a high proton concentration in gastric juice. If this balance is disturbed to give rise to hyperacidity, more or less severe damage to the gastric mucosa can occur, ranging from gastritis to ulceration with resulting pain and other symptoms. The following treatment options are available:

a) **Agents for acid neutralization: antacids.** Laypeople often take sodium bicarbonate (bread soda) to counteract temporary hyperacidity brought on by dietary indiscretions, too much strong coffee, or concentrated alcoholic drinks. It acts immediately, releasing carbon dioxide (which provokes belching) and increasing body sodium. $CaCO_3$, $Mg(OH)_2$, and $Al(OH)_3$ have a more prolonged action without the sodium load. Maalox is a useful combination of $Mg(OH)_2$ and $Al(OH)_3$. $Mg(OH)_2$ on its own has a laxative action and $Al(OH)_3$ is constipating, so in combination these effects cancel each other.

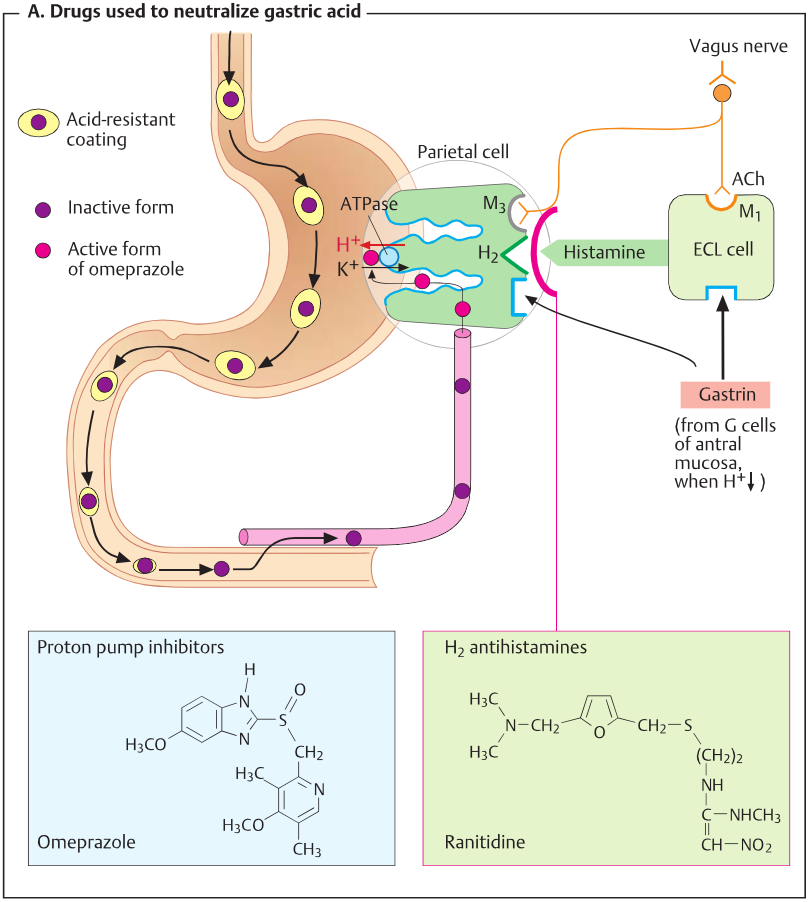
b) **Inhibition of acid production** is necessary when hyperacidity is prolonged and when an ulcer develops. Two groups of drugs are available for this purpose: **H_2 antihistamines and proton pump inhibitors (PPI)**. The antihistamines, which include **ranitidine** and **famotidine**, block histamine-induced stimulation of HCl production in the parietal cells. Cimetidine was the first representative of this group but it inhibits the metabolism of other drugs and is less useful. The introduction of these inhibitors of HCl production represented significant progress. However, **direct inhibition of the Na^+/K^+-ATPase** of the parietal cells is an even more effective method. The first specific inhibitor was **omeprazole**, and analogue substances are now available. When taken orally in gastric juice-resistant capsules, it reaches the parietal cells via the circulation. An active metabolite is produced there in the acid milieu that binds covalently to inhibit the pump. Lansoprazole, pantoprazole, and rabeprazole work the same way. Omeprazole is a racemate; (*S*)-omeprazole (esomeprazole) is now available and is a stronger enantiomer, dose for dose, though this does not provide any therapeutic advantage. A gradual dose-dependent reduction of the acidity of the gastric juice can be achieved with these drugs.

c) When hyperacidity and ulcer disease are suppressed only while omeprazole or similar drugs are taken, colonization of the gastric mucosa by ***Helicobacter pylori*** should be suspected. Specific treatment of this bacterium is then necessary. As shown in ▶ Fig. 25.1**B**, the patient is given a combination of two antibiotics with a proton pump inhibitor for 7 days. The success rate is in excess of 90%. Further infection appears to occur very rarely in adults.

Laxatives

Distension of the intestinal wall by bowel contents stimulates propulsive movements or peristalsis (▶ Fig. 25.3**A**). The distension is registered by receptors and leads to coordinated contraction via the myenteric plexus. Peristalsis can also be stimulated by irritation of the bowel mucosa, e.g., by irritant laxatives.

In the healthy bowel, the frequency of defecation depends on the volume of indigestible fiber in the diet. Constipation occurs when defecation frequency is too low or defecation is associated with straining (hard stools). Before taking laxatives, the possible cause should be investigated medically. Indications for laxative use are: (1) acute evacuation of the entire intestine following oral poisoning in order to reduce the contact time for absorption of the toxin; (2) acute cleansing of the bowel prior to diagnostic and surgical procedures; (3) to reduce straining during defecation in the presence of serious illness (e.g., after myocardial infarction and major surgery); (4) chronic use for anal disorders or hernias; (5) to compensate drugs with a constipating action (e.g., opiates).


A. Drugs used to neutralize gastric acid
Vagus nerve
Acid-resistant coating
Inactive form
Active form of omeprazole
Parietal cell
ATPase
H^+
K^+
M_3
H_2
Histamine
ACh
M_1
ECL cell
Gastrin
(from G cells of antral mucosa, when H^+↓)
Proton pump inhibitors
Omeprazole
H_2 antihistamines
Ranitidine

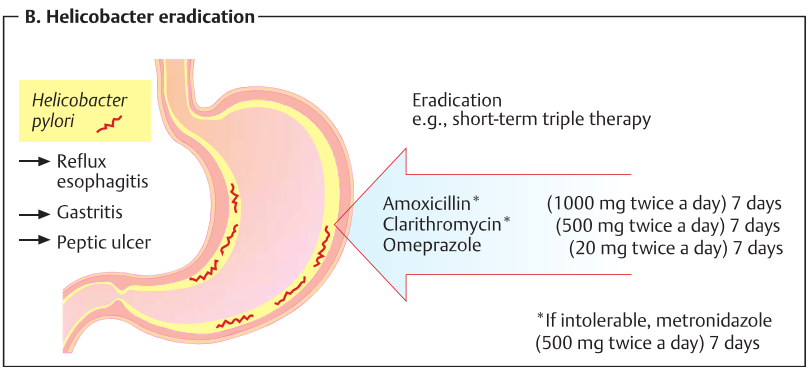

B. Helicobacter eradication
Helicobacter pylori
Reflux esophagitis
Gastritis
Peptic ulcer
Eradication
e.g., short-term triple therapy
Amoxicillin*
Clarithromycin*
Omeprazole
(1000 mg twice a day) 7 days
(500 mg twice a day) 7 days
(20 mg twice a day) 7 days
*If intolerable, metronidazole (500 mg twice a day) 7 days

Fig. 25.1

Rather than prescribing laxatives, physicians should discourage patient self-medication with laxatives, which is based on the discrepancy between the modern low-residue diet and time-honored ideas about the desirable frequency of defecation.

Laxatives can be classified as (1) **bulk laxatives** and (2) **irritant laxatives**. The first group includes **fiber substances** such as bran and linseed, which contain cellulose, and also **osmotically active substances** such as agar-agar and macrogol. Eating whole-grain bread only is also beneficial. Peristalsis can be greatly stimulated by **osmotically active but nonabsorbable salts** such as sodium sulfate and magnesium sulfate (Epsom salt), which retain isotonic water in the bowel. The dosage ranges from a small quantity (daily "drinking cure") to about 20 g for drastic cleansing of the entire intestine. **Lactulose** deserves special mention; lactulose is a nonabsorbable disaccharide with an osmotic action and has a mild laxative effect. It is fermented by colon bacteria and the resulting acidification of the bowel content reduces the number of bacteria (see treatment of hepatic cirrhosis, p. 318).

The **irritant laxative** group consists of castor oil (acting on the small intestine) and anthraquinone derivatives, which act on the colon. **Castor oil** comes from the seed of the castor bean. It is a triglyceride that is cleaved following oral ingestion. Ricinoleic acid is the active agent (▶ Fig. 25.2).

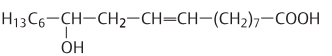


Fig. 25.2

Oral administration of 10–20 mL of castor oil is followed 1–4 hours later by evacuation of the entire bowel. Castor oil is indicated only when there is a particular need for this drastic effect. It is well tolerated. It is not suitable for the treatment of chronic constipation.

Anthraquinone derivatives acting on the large bowel (▶ Fig. 25.4**A**) are indicated whenever soft feces and ease of defecation are required. These substances occur in a variety of plants: senna leaves, buckthorn, and a certain type of rhubarb. In these drugs, the anthraquinone nucleus is bound to a sugar that is cleaved in the colon. It then undergoes further chemical change to emodines, the active substances. These inhibit absorption of water and electrolytes so that soft stool can be passed. The emodines are well tolerated and about 6–8 hours elapse from when they are taken until they have an effect.

Certain **diphenolmethane derivatives** (bisacodyl and sodium picosulfate) have a similar mode of action and also have a longish latency. Potassium and water are lost from the body after these are used.

Chronic laxative use can lead to **dependency**, which is due to a misconception on the user's part. Since the colon is empty after a forced evacuation (▶ Fig. 25.3**B**), it takes a few days with the normal modern diet for the colon to fill sufficiently to allow defecation (▶ Fig. 25.3**B**). This latency is mistaken for constipation. A laxative to stimulate the colon is accordingly taken again and ultimately the user sustains actual damage: so much potassium is lost from the intestine and through the kidneys via the compensatory aldosterone mechanism that hypokalemia develops. Potassium depletion leads to bowel atony so that the user is "obliged" to take a laxative again. An **unnecessary drug side effect** arises because of the patient's inadequate knowledge. This can be cured by professional advice.

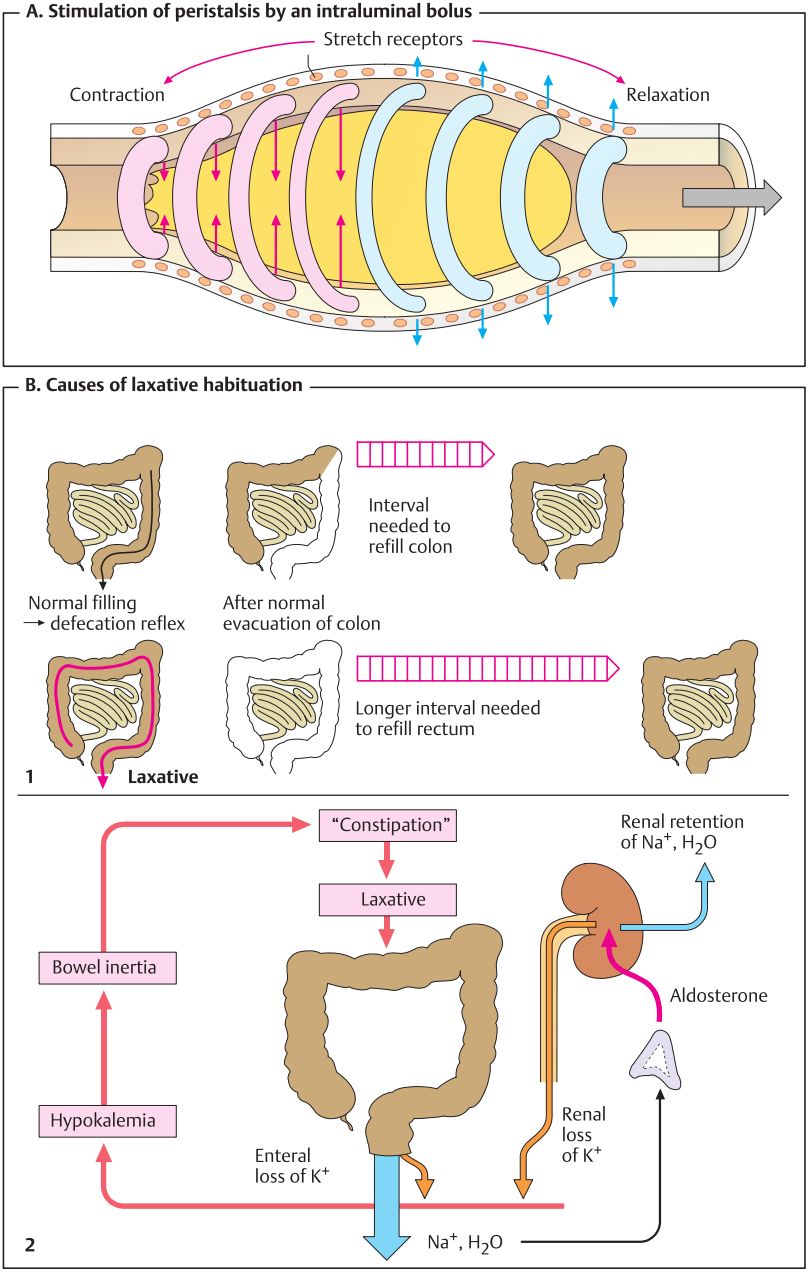

A. Stimulation of peristalsis by an intraluminal bolus
Stretch receptors
Contraction
Relaxation
B. Causes of laxative habituation
Interval needed to refill colon
Normal filling → defecation reflex
After normal evacuation of colon
Longer interval needed to refill rectum
1
Laxative
"Constipation"
Laxative
Bowel inertia
Hypokalemia
Enteral loss of K+
Renal retention of Na+, H2O
Aldosterone
Renal loss of K+
Na+, H2O
2

Fig. 25.3

Antidiarrheal Agents

Diarrhea is the result of excessively fast passage of bowel contents so that absorption of water and electrolytes is inadequate (▶ Fig. 25.4**B**). It can have various causes: (1) Bacterial or viral infections that trigger inflammatory processes. Certain bacteria produce toxins that specifically inhibit certain functions of the gut epithelium, for instance, Na^+/Cl^- cotransport. (2) Poor autonomic control with predominance of propulsive activity over back-and-forth movements (which can have a psychological origin), as a drug side effect and in irritable colon. (3) Bowel dysfunction, defects in defenses against infection that are probably genetic in Crohn disease and ulcerative colitis. (4) Metabolic disorders such as pancreatic insufficiency and steatorrhea.

Diarrhea can sometimes be a harmless disorder (e.g., "traveler's diarrhea") but may have a fatal outcome especially in malnourished children in developing countries; it may also be a symptom of longstanding disease (Crohn disease, ulcerative colitis).

The following agents are available to treat diarrhea; the choice is guided by the cause:

a) Replacement of lost water and salt: **rehydration solutions**. Na^+ and K^+ solutions containing glucose correct losses in dehydrated patients as Na^+/glucose cotransport continues to function even in the presence of bacterial enterotoxin; this is particularly important in cholera.
b) Antibacterial drugs or antibiotics when bacterial infection is found to be the cause of the diarrhea, e.g., cotrimoxazole (▶ Fig. 25.3).
c) Inhibition of propulsive motor activity by an opioid, which slows the onward movement of bowel content through specific receptors in the bowel wall.

Tincture of opium (paregoric) is an age-old remedy that exploited opium's troublesome side effect of constipation. Because of the central "side effects," this therapy has now been abandoned.

New drugs have been developed that inhibit propulsive motor activity by binding to the opioid receptors in the bowel wall but do not have any CNS effects. One such substance is **loperamide** (single dose 2 mg, elimination half-life ~10 hours). Despite the high affinity of loperamide for opioid receptors, there is an interesting reason for its lack of CNS effects: any loperamide that crosses the blood–brain barrier is transported back into the blood by P-glycoproteins.

If degradation of endogenous enkephalins is inhibited in the bowel wall, this also results in slowed propulsive activity. **Racecadotril**, an enkephalinase blocker, acts as an "indirect enkephalin mimetic" and is used to treat diarrhea in babies and small children.

(**d**) Attempts to render bacterial toxins or other toxic substances harmless by **adsorption**. However, large quantities of the adsorbent have to be given orally, e.g., medicinal charcoal 30 mg or more daily, or aluminum silicate 50–100 g daily, which is impractical and unlikely to be successful. Cholestyramine is used in chologenic diarrhea because of its bile acid-binding action.

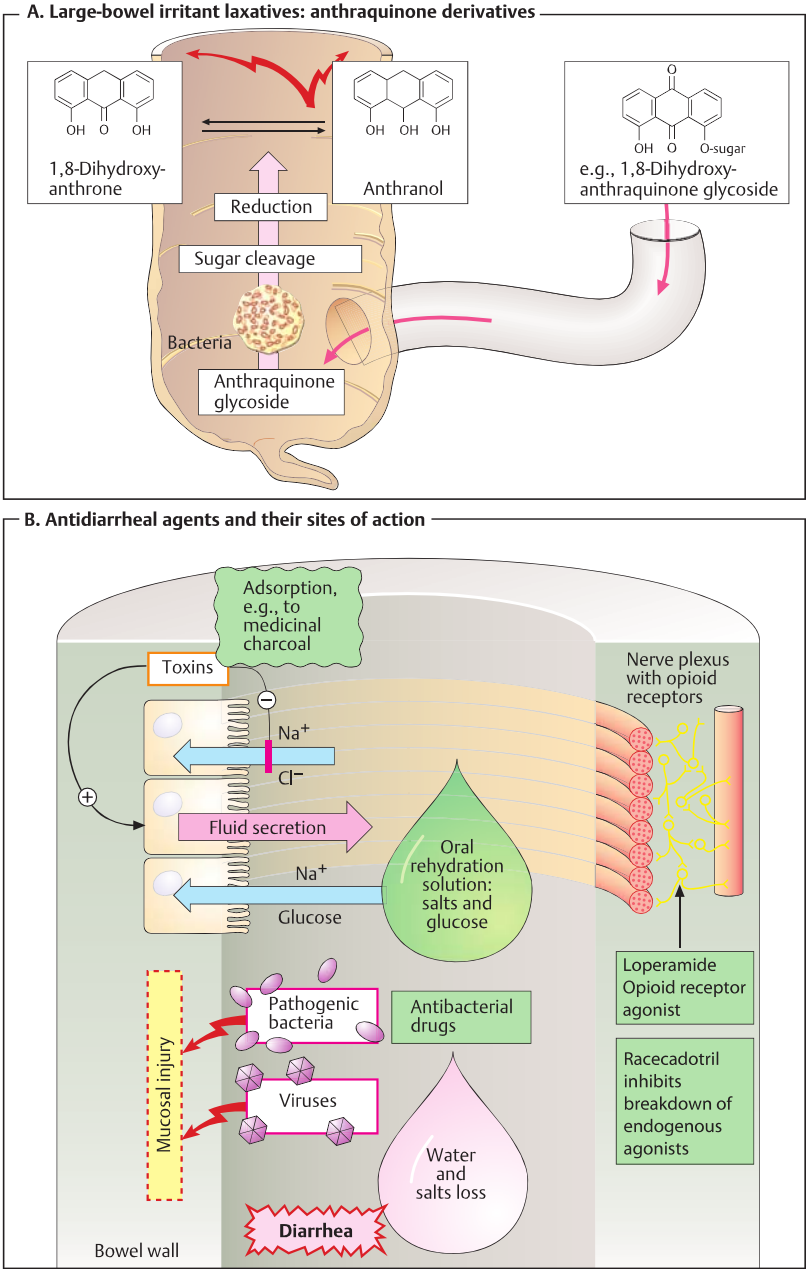

A. Large-bowel irritant laxatives: anthraquinone derivatives
OH O OH
1,8-Dihydroxy-anthrone
OH OH OH
Anthranol
O
OH O O-sugar
e.g., 1,8-Dihydroxy-anthraquinone glycoside
Reduction
Sugar cleavage
Bacteria
Anthraquinone glycoside
B. Antidiarrheal agents and their sites of action
Adsorption, e.g., to medicinal charcoal
Toxins
Nerve plexus with opioid receptors
Na+
Cl−
Fluid secretion
Na+
Glucose
Oral rehydration solution: salts and glucose
Loperamide Opioid receptor agonist
Racecadotril inhibits breakdown of endogenous agonists
Pathogenic bacteria
Antibacterial drugs
Mucosal injury
Viruses
Water and salts loss
Diarrhea
Bowel wall

Fig. 25.4

Drugs Affecting Motor Function

The central part of the **motor system** includes various areas of the cerebral cortex, the basal ganglia, the cerebellum, different nuclei in the brainstem, and the spinal cord. The peripheral part includes the peripheral motor nerves, afferent nerves from muscle spindles, the motor end plate, and finally the skeletal muscle. This section describes the effect of drugs and toxins on spinal and peripheral processes. Disorders of the motor system that originate in higher centers of the CNS, such as epilepsy (p. 336) and Parkinson disease (p. 334), are discussed elsewhere.

Central Muscle Relaxants and Toxins

In the spinal cord, nerve impulses arriving from higher centers or the periphery converge on motor neurons, whose perikarya are located in the anterior horn of the spinal cord. Their axons leave the spine via the anterior roots and course to the muscles. The **motor neurons** obtain information from supraspinal centers through descending tracts and from the periphery through the axons of the spinal ganglia. The information can be transmitted directly or through interneurons. There are also inhibitory **interneurons**, which reduce the excitability of the motor neurons to a physiologically useful level. Thus, the spinal cord possesses a complex network of stimulatory interneurons (transmitter: glutamate) and inhibitory interneurons (transmitters: GABA, glycine).

Impulse transmission in the spinal cord can be affected by drugs and toxins. The sensitivity of the **$GABA_A$ receptor** is increased by benzodiazepines (p. 222), which are allosteric agonists. **Clonazepam** is an example. This increases the effect of the inhibitory interneurons, resulting in a reduction of increased muscle tone. **Baclofen** is a γ-aminobutyric acid derivative with a similar effect through an agonist action on the $GABA_B$ receptor. These substances are collectively termed **central muscle relaxants**.

They are indicated for painful muscle tension or muscle spasm, which can occur in multiple sclerosis and after spinal injuries.

Other inhibitory interneurons including Renshaw cells use **glycine** as transmitter substance. Release of glycine is suppressed by the presence of **tetanus toxin**, so that damping of the motor neurons, which is necessary physiologically, is abolished. The result is tetanic muscle convulsions. The alkaloid **strychnine** is a direct antagonist at the glycine receptor. This mechanism also leads to disinhibition of the motor neurons and thus to muscle spasms.

Acetylcholine (ACh) is synthesized by the enzyme ACh synthetase in the ends of motor nerve axons and is stored in vesicles that accumulate close to the presynaptic membrane. The vesicles adjacent to the membrane are attached to binding proteins, which prevent fusion with the plasmalemma. It is only when an action potential reaches the nerve ending that the influx of Ca^{2+} ions enables the vesicles to fuse with the plasmalemma and release their ACh. Botulinum toxin destroys one of the exocytosis proteins (SNAP-25) enzymatically. This results in paralysis of skeletal muscle. Acetylcholine release is boosted in *Lambert-Eaton syndrome*, a disease characterized by muscle weakness. Antibodies to Ca^{2+} channel proteins weaken nerve ending excitability. *Amifampridine* is able to increase their excitability by blocking K^+ channels.

The postsynaptic membrane of the muscle fiber is highly folded to increase its surface area. The surface is occupied by ACh receptors of the nicotinic type (see p. 120). ACh esterase molecules are anchored in the basal lamina, which fills the synaptic gap. The ACh released by the nerve impulse occupies the ACh receptors briefly and is immediately inactivated biologically by ester cleavage. This means that the action of ACh is completed after only a few milliseconds. Occupation of the ACh receptors reduces the membrane potential for 1–2 milliseconds, thereby producing a propagated action potential, which spreads out over the entire muscle fiber and triggers contraction.

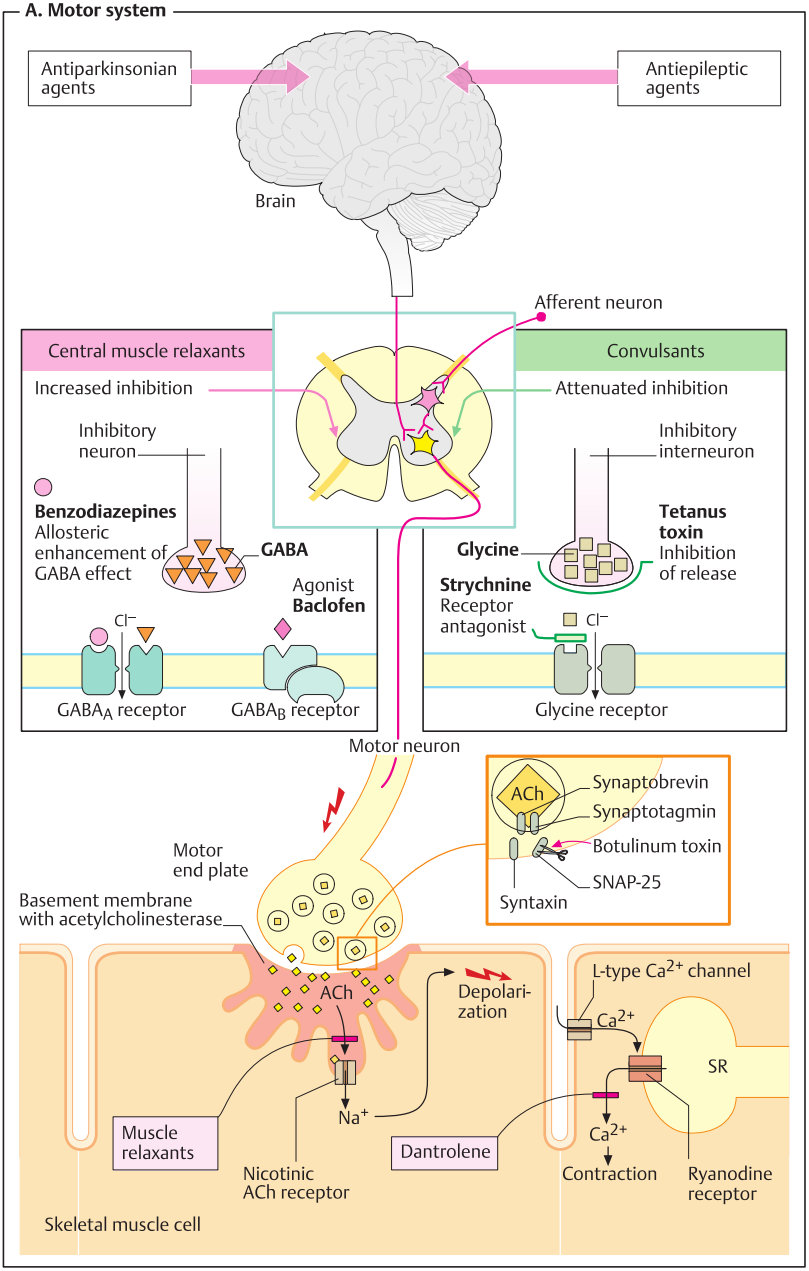

A. Motor system
Antiparkinsonian agents
Antiepileptic agents
Brain
Afferent neuron
Central muscle relaxants
Increased inhibition
Inhibitory neuron
Benzodiazepines
Allosteric enhancement of GABA effect
GABA
Agonist
Baclofen
Cl⁻
GABA$_A$ receptor
GABA$_B$ receptor
Convulsants
Attenuated inhibition
Inhibitory interneuron
Tetanus toxin
Inhibition of release
Glycine
Strychnine
Receptor antagonist
Cl⁻
Glycine receptor
Motor neuron
ACh
Synaptobrevin
Synaptotagmin
Botulinum toxin
SNAP-25
Syntaxin
Motor end plate
Basement membrane with acetylcholinesterase
ACh
Depolarization
L-type Ca^{2+} channel
Ca^{2+}
SR
Na$^+$
Muscle relaxants
Nicotinic ACh receptor
Dantrolene
Ca^{2+}
Contraction
Ryanodine receptor
Skeletal muscle cell

Fig. 26.1

Muscle Relaxants

The need to produce flaccid paralysis of skeletal musculature arose with the development of modern medicine. It is essential for artificial ventilation. Prolonged anesthesia can no longer be imagined without muscle relaxation and ventilation. The function of the motor end plate can be interrupted reversibly by two mechanisms at receptor level: (a) by an agonist, which triggers a single action potential in the adjacent membrane after binding but then remains bound there, keeping the end plate membrane depolarized: **depolarizing muscle relaxants**; (b) by acting as an antagonist at the ACh receptor: **nondepolarizing muscle relaxants**.

Depolarizing Muscle Relaxants

The simplest chemical substance that paralyzes muscle by long-acting depolarization is **decamethonium**:

$$(CH_3)_3N^+-(CH_2)_{10}-N^+(CH_3)_3 \qquad (26.1)$$

This is constructed of a hydrocarbon chain with two positively charged nitrogen atoms separated by a distance of ~1 nm. The metabolically stable decamethonium was used in anesthesia but was abandoned because of its poor pharmacokinetics. It has the typical basic structure of all muscle relaxants. Suxamethonium (succinylcholine) also has this structure.

Succinylcholine can be described as a double ACh molecule. It has affinity for the nicotinic ACh receptor but cannot be broken down by specific acetylcholinesterase. Nonspecific serum cholinesterase cleaves succinylcholine slowly, so that an active concentration is maintained in the synaptic cleft for 5–10 minutes (for comparison the duration of action of ACh is 1–2 milliseconds).

Depolarization of the end plate initially triggers a propagated action potential in the surrounding muscle cell membrane, leading to contraction of the muscle fiber; fine muscle twitches can be observed briefly following i.v. injection.

A new action potential (AP) can be elicited near the end plate only if the membrane has not been excited in the meantime and allowed to repolarize. The AP is due to opening of the Na^+ channel proteins, allowing Na^+ ions to flow through the sarcolemma and cause depolarization. After a few milliseconds, the Na^+ channels close automatically ("inactivation"), the membrane potential returns to resting levels and the AP is terminated. As long as the membrane potential remains incompletely repolarized, renewed opening of the Na^+ channels and thus a further AP is impossible. In the case of released ACh, rapid breakdown by acetylcholinesterase allows repolarization of the end plate and thus a return of Na^+ channel excitability in the surrounding sarcolemma. With succinylcholine, however, there is persistent depolarization of the end plate and adjoining membrane regions. Because the Na^+ channels remain inactivated, an AP cannot be triggered in the adjacent membrane.

Side effects of succinylcholine are a rise in the serum potassium concentration with possible consequences for cardiac function, and a rise in blood pressure and tachycardia induced by ganglionic stimulation. The multifocally innervated tonic fibers of the extrinsic ocular muscles contract in reaction to succinylcholine, leading to an increase of pressure in the eyeball. Succinylcholine must therefore not be used before intraocular surgery. Moreover, chronically denervated muscles develop contracture because ACh receptors develop over the entire surface of denervated skeletal muscle fibers after their motor nerve has been severed. This contracture, together with the corresponding potassium loss, is likely to occur in trauma patients undergoing "follow-up" surgery.

The **advantage** of succinylcholine is its very rapid onset of action. Since some nondepolarizing muscle relaxant drugs have recently been found to have a rapid onset of action, use of succinylcholine has diminished. It remains the most important relaxant for emergency intubation.

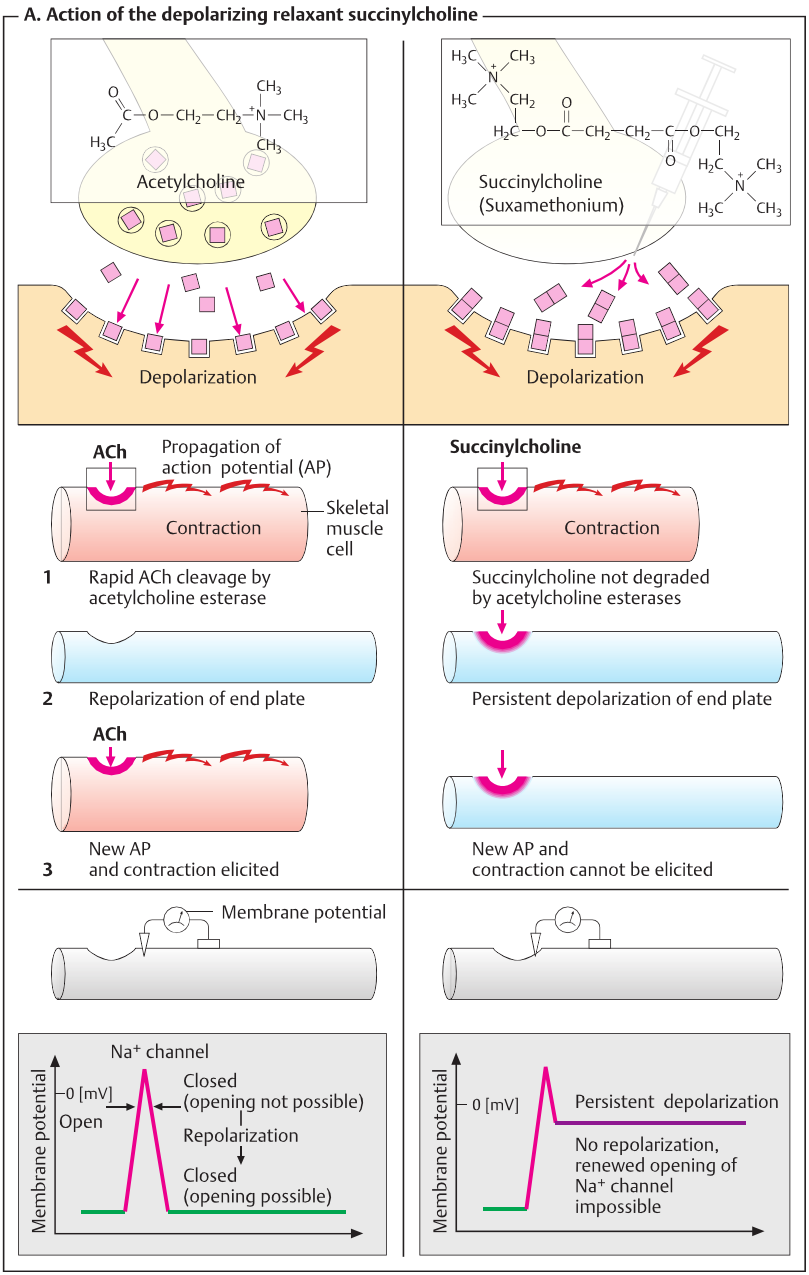

A. Action of the depolarizing relaxant succinylcholine
Acetylcholine
Succinylcholine (Suxamethonium)
Depolarization
Depolarization
ACh
Propagation of action potential (AP)
Contraction
Skeletal muscle cell
Succinylcholine
Contraction
1
Rapid ACh cleavage by acetylcholine esterase
Succinylcholine not degraded by acetylcholine esterases
2
Repolarization of end plate
Persistent depolarization of end plate
ACh
3
New AP and contraction elicited
New AP and contraction cannot be elicited
Membrane potential
Na+ channel
Membrane potential
0 [mV]
Open
Closed (opening not possible)
Repolarization
Closed (opening possible)
Membrane potential
0 [mV]
Persistent depolarization
No repolarization, renewed opening of Na+ channel impossible

Fig. 26.2

Nondepolarizing Muscle Relaxants

Muscle-relaxing poisons have long played a part in human history. The poisoned arrows used by the indigenous people of South America killed animals by muscle paralysis. However, the meat of the killed animals could be consumed without danger as the muscle poisons are not absorbed from the gastrointestinal tract.

These muscle relaxants have a more complex chemical structure than decamethonium. The nondepolarizing muscle relaxants also possess the two crucial positively charged nitrogen atoms, but these are in a ring system. The two N-containing rings are linked either by a long aliphatic chain or by a steroid structure. The formulas of two synthetic muscle relaxants are illustrated in ▶ Fig. 26.3**A**. These large molecules have high binding affinity for the nicotinic ACh receptor but have no intrinsic activity; that is, they are pure antagonists.

The ingredient of curare, *d*-tubocurarine, is no longer used in anesthesia because it can produce unpleasant side effects: histamine release with a drop in blood pressure, bronchospasm, and increased secretion in the bronchial tree. A ganglion-blocking effect is also apparent. The new synthetic relaxants are better tolerated. They differ in their **pharmacokinetic properties** such as speed of onset of action and duration of action. The following drugs are used in surgery: **pancuronium** (long-acting), **vecuronium** (medium-acting), **mivacurium** (short-acting), **rocuronium** (fast onset of action), and **atracurium** (undergoes spontaneous cleavage after administration and does not require metabolic degradation, important for patients with liver disease).

The action of the nondepolarizing muscle relaxants can be shortened by giving an ACh esterase inhibitor such as neostigmine (see p. 122). The ACh released in the end plate is no longer broken down and accumulates in the synaptic cleft. The ratio of antagonist to agonist improves in favor of the transmitter.

Sugammadex embodies a different principle for terminating muscle relaxation. This γ-cyclodextrin forms a molecular cage in which it "traps" rocuronium and vecuronium, inactivates them, and finally eliminates them via the kidneys.

Finally, it should be noted that the muscle relaxants are unable to penetrate the CNS, which means that the "relaxed" patient would be wide awake and would immediately become dramatically hypoxic due to paralysis of the respiratory muscles, while being totally unable to communicate because all muscles would be paralyzed. **Anesthesia and artificial ventilation are essential whenever muscle relaxants are used**.

In discussing muscle relaxants, a poison that produces muscle paralysis by inhibiting ACh release in the motor end plate should be mentioned. This is **botulinum toxin** from *Clostridium botulinum*. After passing through the presynaptic membrane, it inactivates the process of fusion of ACh vesicles with the membrane (p. 190). Botulinum toxin is an extraordinarily potent poison. The effect lasts a long time as the affected end plate has been irreversibly damaged. Re-innervation has to take place by growth of a new axon ending. This toxin is used as a drug. It can be injected into muscle to treat painful muscle spasms such as blepharospasm. It is also used in cosmetic medicine for the currently fashionable face lifting.

Influencing the Contractile System

The action potential briefly depolarizes the plasmalemma of muscle cells including the tubular structures. This releases Ca^{2+} from the transverse tubules, which then produces shortening of actomyosin. This is known as electromechanical coupling. This process can be inhibited by **dantrolene**, which is used to treat painful muscle spasms and malignant hyperthermia.

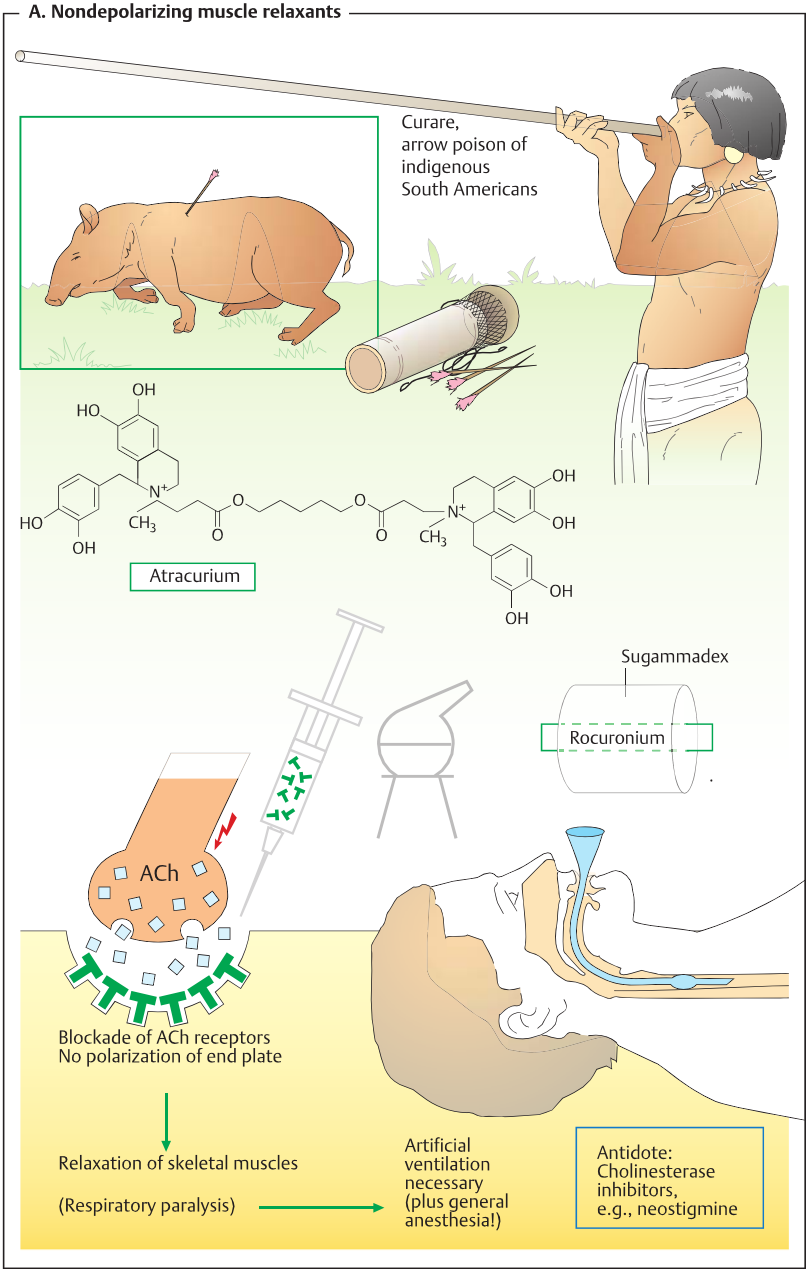

A. Nondepolarizing muscle relaxants
Curare, arrow poison of indigenous South Americans
Atracurium
Sugammadex
Rocuronium
ACh
Blockade of ACh receptors
No polarization of end plate
Relaxation of skeletal muscles
(Respiratory paralysis)
Artificial ventilation necessary (plus general anesthesia!)
Antidote: Cholinesterase inhibitors, e.g., neostigmine

Fig. 26.3

Pain Mechanisms and Pathways

Pain is a designation for a spectrum of sensations of highly divergent character and intensity ranging from unpleasant to intolerable. Pain stimuli are detected by physiological receptors (sensors, nociceptors) least differentiated morphologically, viz., free nerve endings. The body of the bipolar afferent first-order neuron lies in the dorsal root ganglion. Nociceptive impulses are conducted via unmyelinated (C-fibers, conduction velocity 0.2–2 m/s) and myelinated axons (Aδ-fibers, 10–30 m/s). The free endings of Aδ-fibers respond to intense pressure or heat, those of C-fibers respond to chemical stimuli (H^+, K^+, histamine, bradykinin, etc.) arising from tissue trauma.

Irrespective of whether chemical, mechanical, or thermal stimuli are involved, they become significantly more effective in the presence of prostaglandins (p. 198).

Chemical stimuli also underlie pain secondary to inflammation or ischemia (angina pectoris, myocardial infarction). The intense pain that occurs during overdistension or spasmodic contraction of smooth muscle abdominal organs may be maintained by local anoxemia developing in the area of spasm (visceral pain).

Aδ- and C-fibers enter the spinal cord via the dorsal root, ascend in the dorsolateral funiculus, and then synapse on second-order neurons in the dorsal horn. The axons of the second-order neurons cross the midline and ascend to the brain as the anterolateral pathway or spinothalamic tract. Based on phylogenetic age, a neospinothalamic tract and a paleospinothalamic tract are distinguished. The second-order (projection) neurons of both tracts lie in different zones (laminae) of the dorsal horn. Lateral thalamic nuclei receiving neospinothalamic input project to circumscribed areas of the postcentral gyrus. Stimuli conveyed via this path are experienced as sharp, clearly localizable pain. The medial thalamic regions receiving palaeospinothalamic input project to the postcentral gyrus as well as the frontal, limbic cortex and most likely represent the pathway subserving pain of a dull, aching, or burning character, i.e., pain that can be localized only poorly.

Impulse traffic in the neospinothalamic and paleospinothalamic pathways is subject to modulation by descending projections that originate from the reticular formation and terminate at second-order neurons, at their synapses with first-order neurons or spinal segmental interneurons (**descending antinociceptive system**). This system can inhibit substance P-mediated impulse transmission from first- to second-order neurons via release of endogenous opiopeptides (enkephalins) or monoamines (norepinephrine, serotonin).

Pain sensation can be influenced or modified as follows:

- Elimination of the cause of pain
- Lowering of the **sensitivity of nociceptors** (antipyretic analgesics, local anesthetics)
- Interrupting **nociceptive conduction** in sensory nerves (local anesthetics)
- Suppression of **transmission of nociceptive impulses** in the spinal medulla (opioids)
- Inhibition of **pain perception** (opioids, general anesthetics)
- Altering emotional responses to pain, i.e., pain behavior (antidepressants as coanalgesics).

Neuropathic pain is severe and chronic, and hardly responds at all to the usual analgesics. It may occur as a complication of diabetes mellitus or herpes zoster or as phantom pain. It is known that new (embryonic) and overactive Na^+ channels can appear on afferent C-fibers following trauma and these generate spontaneously propagated excitation. Combined long-term treatment with antidepressants (e.g., amitriptyline), anticonvulsants (e.g., gabapentin) and possibly a low-dose opioid (tramadol) may be helpful.

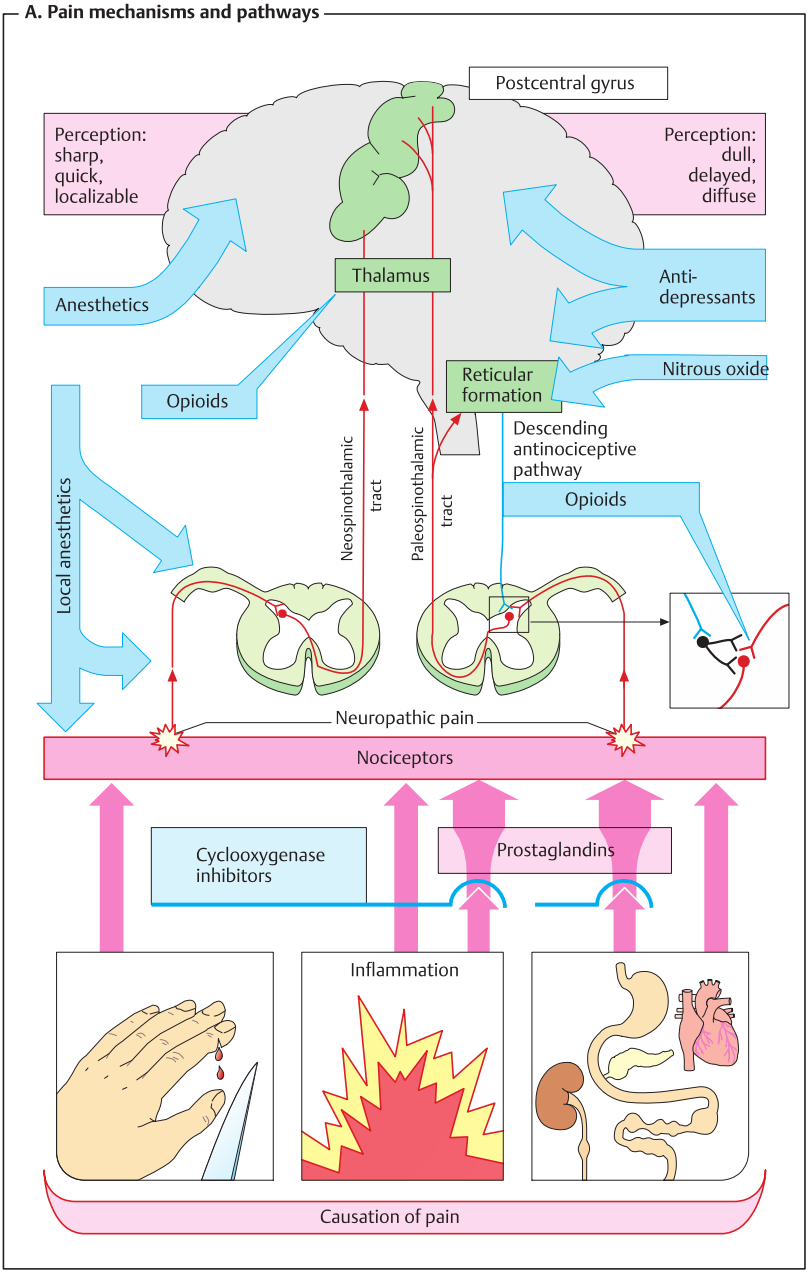

A. Pain mechanisms and pathways
Postcentral gyrus
Perception: sharp, quick, localizable
Perception: dull, delayed, diffuse
Thalamus
Anesthetics
Anti-depressants
Opioids
Reticular formation
Nitrous oxide
Descending antinociceptive pathway
Opioids
Local anesthetics
Neospinothalamic tract
Paleospinothalamic tract
Neuropathic pain
Nociceptors
Cyclooxygenase inhibitors
Prostaglandins
Inflammation
Causation of pain

Fig. 27.1

Eicosanoids

Under the influence of cyclooxygenases (COX-1, COX-2, and their splice variants), the extended molecule of arachidonic acid (eicosatetraenoic acid[1]) is converted into compounds containing a central ring with two long substituents: prostaglandins, prostacyclin, and thromboxanes. Via the action of a lipoxygenase, arachidonic acid yields leukotrienes, in which ring closure in the center of the molecule (▶ Fig. 27.2**A**) does not occur. The products formed from arachidonic acid are inactivated very rapidly; they act as **local hormones**. The groups of prostaglandins and leukotrienes each comprise a large number of closely related compounds. In the present context, only the most important prostaglandins and their constitutive actions are considered.

Prostaglandin (PG)E_2 inhibits gastric acid secretion and increases production of mucus (mucosa-protective action). **$PGF_{2\alpha}$** stimulates uterine motility. **PGI_2** (prostacyclin) produces vasodilatation and promotes renal excretion of Na^+. In addition, prostaglandins synthesized by COX-2 participate in inflammatory processes by sensitizing nociceptors, thus lowering pain threshold; by promoting inflammatory responses by release of mediators such as interleukin-1 and tumor-necrosis factor **α**; and by evoking fever.

Prostacyclin is produced in vascular endothelium and plays a role in the regulation of blood flow. It elicits vasodilation and prevents aggregation of platelets (functional antagonist of thromboxane).

Thromboxane A_2 is a local hormone of platelets; it promotes their aggregation. Small defects in the vascular or capillary wall elicit the formation of thromboxane.

Leukotrienes[2] are produced mainly in leukocytes and mast cells. Newly formed leukotrienes can bind to glutathione. From this complex, glutamine and glycine can be cleaved, resulting in a larger number of local hormones. Leukotrienes are pro-inflammatory; they stimulate invasion of leukocytes and enhance their activity. In anaphylactic reactions, they produce vasodilation, increase vascular permeability, and cause vasoconstriction.

▶ **Therapeutic uses of synthetic eicosanoids.** Efforts to synthesize stable derivatives of prostaglandins for therapeutic applications have not been very successful to date. Dinoprostone (PGE2), gemeprost, and sulprostan are uterine stimulants (p. 144). Misoprostol is meant to afford protection of the gastric mucosa but has pronounced systemic side effects. All these substances lack organ specificity.

[1] Name derived from Greek *eikosi* = twenty for the number of carbon atoms and *tetra* = 4 for the number of double bonds

[2] Note the change in chemical nomenclature: *-triene* (tri = three), although leukotrienes possess four double bonds; however, of these only the conjugated ones are counted

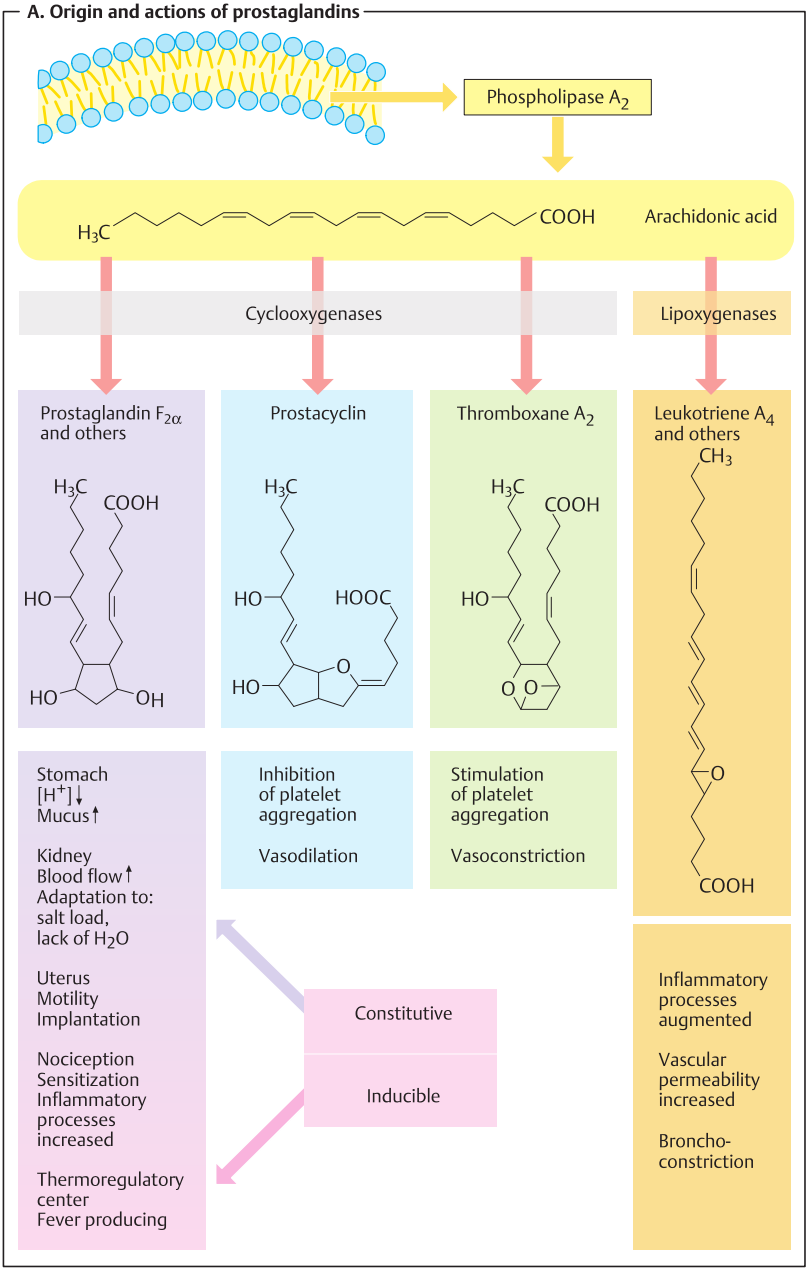

A. Origin and actions of prostaglandins
Phospholipase A2
H3C
COOH
Arachidonic acid
Cyclooxygenases
Lipoxygenases
Prostaglandin F2α and others
Prostacyclin
Thromboxane A2
Leukotriene A4 and others
HO
HOOC
OH
CH3
O
Stomach
[H+]↓
Mucus↑
Kidney
Blood flow↑
Adaptation to:
salt load,
lack of H2O
Uterus
Motility
Implantation
Nociception
Sensitization
Inflammatory processes increased
Thermoregulatory center
Fever producing
Inhibition of platelet aggregation
Vasodilation
Stimulation of platelet aggregation
Vasoconstriction
Inflammatory processes augmented
Vascular permeability increased
Broncho-constriction
Constitutive
Inducible

Fig. 27.2

Analgesics

The large and important family of drugs for the treatment of pain, inflammation, and fever has to be subdivided into two groups that differ in their mechanism of action and spectrum of activity, namely,

- Antipyretic analgesics
- Nonsteroidal anti-inflammatory drugs (NSAIDs)

Antipyretic Analgesics

These analgesics have clinically useful analgesic and antipyretic efficacy. Their mechanism of action is not completely understood but thought to be mediated via inhibition of prostanoid formation by variants of COX enzymes. Acetaminophen (paracetamol), phenazone, and metamizole belong in this group.

Acetaminophen has good analgesic efficacy in commonplace pain, such as toothache and headaches, but is of less use in inflammatory and visceral pain. It exerts a strong antipyretic effect. The adult dosage is 0.5–1.0 g up to four times daily; the elimination half-life is about 2 hours. Acetaminophen is eliminated renally after conjugation to sulfuric or glucuronic acid. A small portion of the dose is converted by hepatic CYP450 to a reactive metabolite that requires detoxification by coupling to glutathione. In suicidal or accidental poisoning with acetaminophen (10 g), the depleted store of thiol groups must be replaced by administration of acetylcysteine as quickly as possible. This measure can be life-saving. Lower doses of acetaminophen should be used if there has been previous liver damage. Long-term therapy with pure acetaminophen preparations does not cause renal damage, reported earlier after use of stimulant combination preparations. Fixed combinations with codeine may be used with hardly any reservation (e.g., Solpadeine tablets).

Dipyrone (metamizole) is a pyrazolone derivative. It produces strong analgesia, even in pain of colic, and has an additional spasmolytic effect. The antipyretic effect is marked. The usual dosage is about 500 mg orally. Higher doses (up to 2.5 g) are needed for biliary colic. The effect of a standard dose lasts ~ 6 hours.

Use of dipyrone is compromised by a very rare but serious adverse reaction, viz., bone marrow depression. The incidence of agranulocytosis remains controversial; probably, one case occurs in > 100 000 treatments. Circulatory shock may occur after rapid intravenous injection. **Dipyrone is not for routine use**; however, short-term administration is recommended for appropriate individual cases.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

This term subsumes drugs that (a) are characterized chemically by an acidic moiety (not present in COX-2 inhibitors) linked to an aromatic residue; and that (b) by virtue of inhibiting cyclooxygenases, are effective in suppressing inflammation, alleviating pain, and lowering fever. Cyclooxygenases (COX) localized to the endoplasmic reticulum are responsible for the formation from arachidonic acid of a group of local hormones comprising the prostaglandins, prostacyclin, and thromboxanes. NSAIDs (except ASA) are reversible inhibitors of COX enzymes. These enzymes possess an elongated pore into which the substrate arachidonic acid is inserted and converted to an active product. NSAIDs penetrate into this pore and thus prevent access for arachidonic acid, leading to reversible blockade of the enzyme.

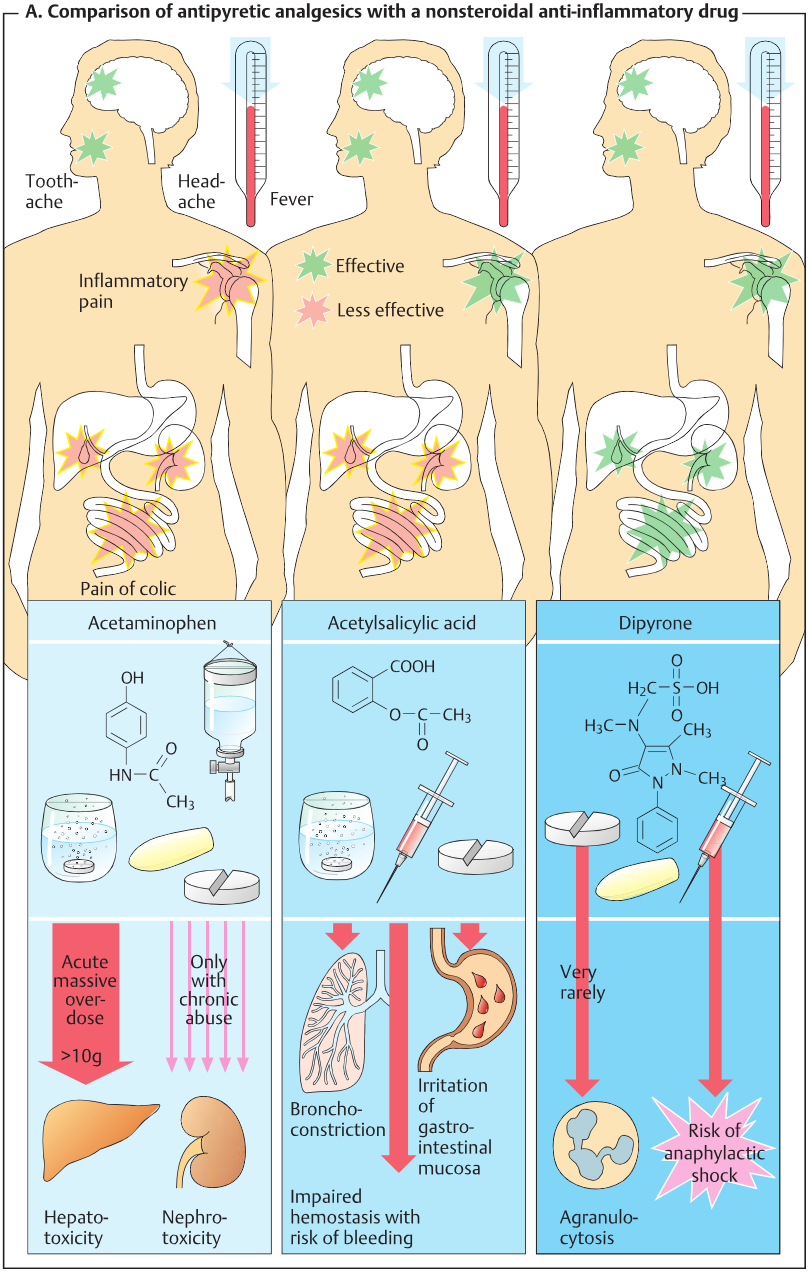

A. Comparison of antipyretic analgesics with a nonsteroidal anti-inflammatory drug
Tooth-ache
Head-ache
Fever
Inflammatory pain
Effective
Less effective
Pain of colic
Acetaminophen
OH
HN—C
O
CH3
Acute massive over-dose
>10g
Only with chronic abuse
Hepato-toxicity
Nephro-toxicity
Acetylsalicylic acid
COOH
O—C—CH3
O
Broncho-constriction
Irritation of gastro-intestinal mucosa
Impaired hemostasis with risk of bleeding
Dipyrone
H2C—S—OH
H3C—N
CH3
N
CH3
Very rarely
Risk of anaphylactic shock
Agranulo-cytosis

Fig. 27.3

Two principal types of cyclooxygenase (COX) can be distinguished:

1. **COX-1** is constitutive, that is, always present and active; it contributes to the physiological function of organs. Inhibition inevitably produces unwanted effects, such as mucosal injury, renal damage, hemodynamic changes, and disturbances of uterine function.
2. **COX-2** is induced by inflammatory processes and produces prostaglandins that sensitize nociceptors, evoke fever, and promote inflammation by causing vasodilation and an increase in vascular permeability. However, in some organs, COX-2 is also expressed constitutively (kidney, vascular endothelium, uterus, and CNS).

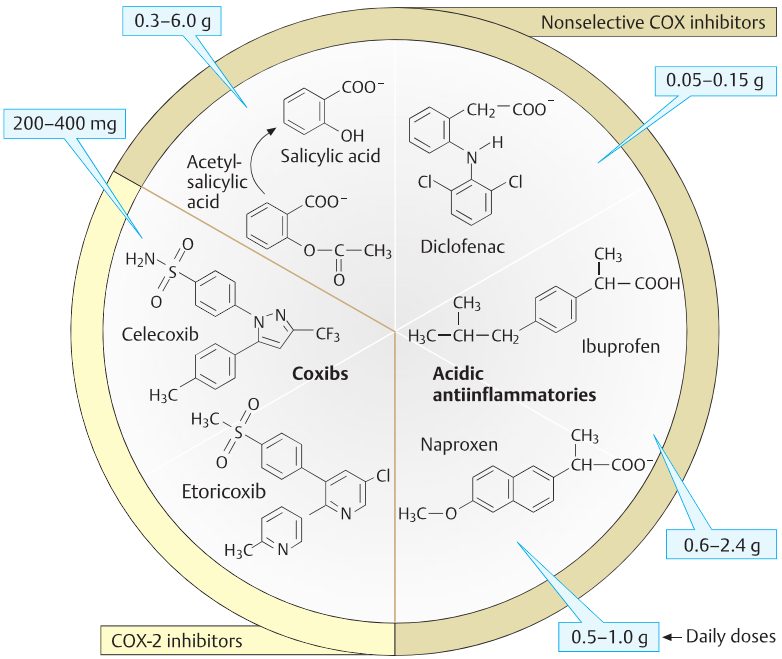
Nonselective COX inhibitors are derived from an acid (acetic or propionic acid) bound to an aromatic residue. Apart from acetylsalicylic acid, the most important drugs in this group are naproxen, ibuprofen, diclofenac, and indomethacin. They have a wide range of indications, including rheumatic diseases and all types of pain; they reduce fever and have an anti-inflammatory action. Ibuprofen and naproxen are best tolerated, and diclofenac is the most effective.

Acetylsalicylic acid (**ASA**) can be used for the same indications as the other nonsteroidal anti-inflammatory drugs. It merits a separate comment. Acetylation of salicylic acid significantly reduces its ability to induce mucosal injury. After absorption of ASA, the acetyl moiety is cleaved with a half-life of 15–20 minutes, so that salicylic acid is then present in vivo. The dosage of ASA required for anti-inflammatory therapy is over 3 g daily. About 500 mg is needed to relieve ordinary pain. At low dosage (100–200 mg daily), following absorption into the portal circulation, ASA causes a long-lasting blockade of COX-1-mediated thromboxane synthesis in platelets because of irreversible acetylation of the enzyme. Since platelets are cell fragments without a nucleus, they are unable to synthesize new COX molecules.

Acetylsalicylic acid can cause major side effects. It irritates the gastric mucosa and can cause asthma in predisposed patients. ASA must not be combined with phenprocoumon because of the additive effect and should not be taken in late pregnancy as it can cause weak labor, a risk of hemorrhage in mother and baby, and premature closure of the ductus arteriosus in the infant.

The **COX-2 inhibitors** aroused great expectations because gastric tolerability was supposed to be much better since only COX-2 is inhibited. Large quantities of the COX-2 inhibitors were then prescribed until it became apparent that they had major side effects. Some of the new top sellers, such as rofecoxib (Vioxx®), had to be withdrawn from the market. An increased incidence of thromboembolic events such as myocardial infarction and stroke was observed after prolonged use of rofecoxib. This was probably due to preponderance of thromboxane A_2 production in platelets by COX-1 at the same time that COX-2-mediated production of prostacyclin in the endothelium was being inhibited. Lumaricoxib (liver damage) and valdecoxib (skin reactions) were also withdrawn. Currently (2017), three COX-2 inhibitors are still available, but with restrictions; these are oral celecoxib and etoricoxib for the treatment of degenerative and rheumatic joint pain, and intravenous parecoxib for postoperative pain.

A. Nonsteroidal anti-inflammatory drugs (NSAIDs)



B. Adverse effects of nonsteroidal anti-inflammatory drugs

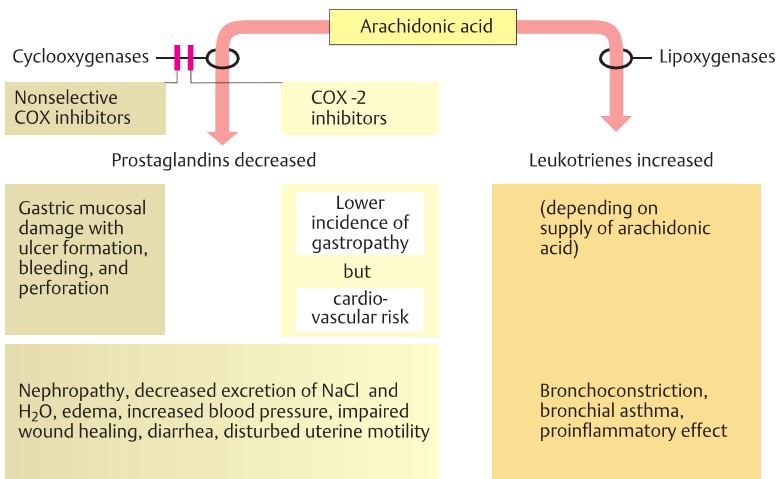

Arachidonic acid
Cyclooxygenases
Lipoxygenases
Nonselective COX inhibitors
COX -2 inhibitors
Prostaglandins decreased
Leukotrienes increased
Gastric mucosal damage with ulcer formation, bleeding, and perforation
Lower incidence of gastropathy
but
cardio-vascular risk
(depending on supply of arachidonic acid)
Nephropathy, decreased excretion of NaCl and H_2O, edema, increased blood pressure, impaired wound healing, diarrhea, disturbed uterine motility
Bronchoconstriction, bronchial asthma, proinflammatory effect

Fig. 27.4

Local Anesthetics

Local anesthetics reversibly inhibit impulse generation and propagation in nerves. In sensory nerves, such an effect is desired when painful procedures must be performed, e.g., surgical or dental operations.

► **Mechanism of action.** Axonal impulse conduction occurs in the form of an action potential. The change in potential involves a rapid influx of Na^+ (► Fig. 27.5**A**) through a membrane channel protein that, upon being opened (activated), permits rapid inward movement of Na^+ down a chemical gradient ($[Na^+]_{outside}$ ~ 150 mM, $[Na^+]_{inside}$ ~7 mM). Local anesthetics are capable of inhibiting this rapid influx of Na^+; initiation and propagation of excitation are therefore blocked (► Fig. 27.5**A**).

Na^+ channels consist of a protein with four subunits, each consisting of six transmembrane segments (S1–S6) (► Fig. 27.5**A**). Segments S5 and S6 of the four domains constitute the ion-conducting pores (blue), which can also be identified in the crystal structure of a Na^+ channel protein. Due to depolarization of the cell membrane, the positively charged S4 segments of the channel move and this causes opening of the channel and influx of Na^+ into the cell (green arrow). Local anesthetics (red arrow) diffuse from the extracellular space into the axon, penetrate into the channel from the cytosol, and block Na^+ influx.

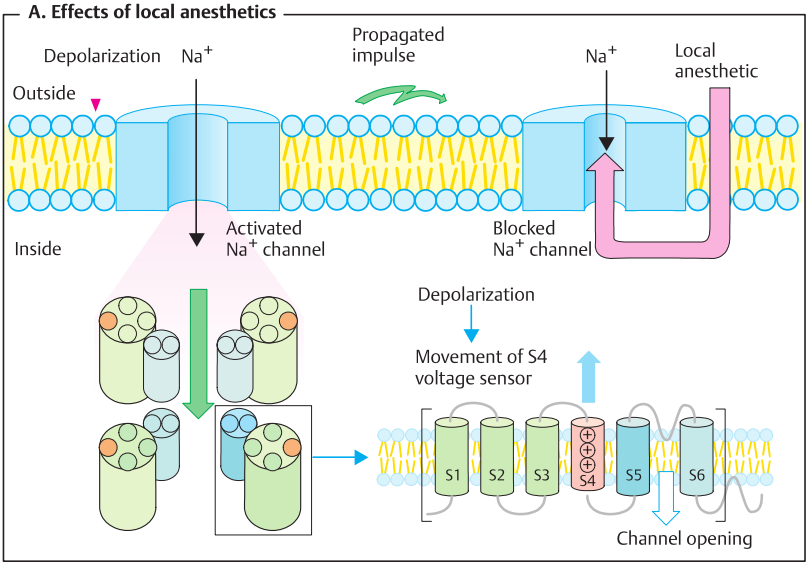
Local anesthetic activity is also shown by uncharged substances, suggesting a binding site in nonpolar regions of the channel protein or the surrounding lipid membrane.

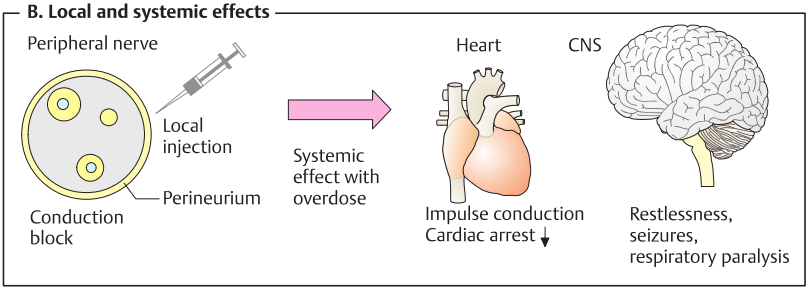
► **Mechanism-specific adverse effects.** Since local anesthetics block Na^+ influx not only in sensory nerves but also in other excitable tissues (► Fig. 27.5**A**), they are administered locally. Depression of excitatory processes in the heart, while undesired during local anesthesia, can be used therapeutically in cardiac arrhythmias (p. 150).

► **Forms of local anesthesia.** Local anesthetics are administered via different routes, including infiltration of the tissue (**infiltration anesthesia**) or injection next to the nerve branch carrying fibers from the region to be anesthetized (**conduction anesthesia** of the nerve, **spinal anesthesia** of segmental dorsal roots), or by application to the surface of the skin or mucosa (**surface anesthesia**). In each case, the local anesthetic drug is required to diffuse to the nerves concerned from a depot placed in the tissue or on the skin.

► **High sensitivity of sensory, low sensitivity of motor nerves.** Impulse conduction in sensory nerves is inhibited at a concentration lower than that needed for motor fibers. This difference may be due to the higher impulse frequency and longer action potential duration in nociceptive as opposed to motor fibers. Alternatively, it may relate to the thickness of sensory and motor nerves, as well as the distance between the nodes of Ranvier. In saltatory impulse conduction, only the nodal membrane is depolarized. Because depolarization can still occur after blockade of three or four nodal rings, the area exposed to a drug concentration sufficient to cause blockade must be larger for motor fibers (► Fig. 27.5**B**).

This relationship explains why sensory stimuli that are conducted via myelinated Aδ-fibers are affected later and to a lesser degree than are stimuli conducted via unmyelinated C-fibers. Since autonomic postganglionic fibers lack a myelin sheath, they are susceptible to blockade by local anesthetics. As a result, vasodilation ensues in the anesthetized region, because sympathetically driven vasomotor tone decreases. This local vasodilation is undesirable.


A. Effects of local anesthetics
Depolarization
Na+
Propagated impulse
Na+
Local anesthetic
Outside
Inside
Activated Na+ channel
Blocked Na+ channel
Depolarization
Movement of S4 voltage sensor
S1
S2
S3
S4
S5
S6
Channel opening


B. Local and systemic effects
Peripheral nerve
Local injection
Perineurium
Conduction block
Systemic effect with overdose
Heart
Impulse conduction
Cardiac arrest
CNS
Restlessness, seizures, respiratory paralysis

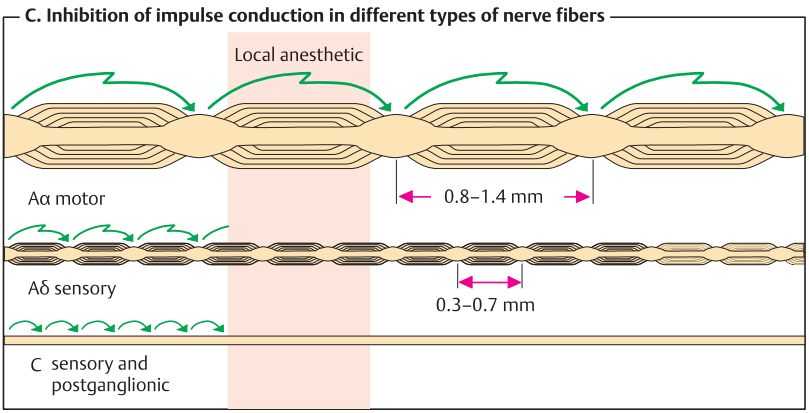

C. Inhibition of impulse conduction in different types of nerve fibers
Local anesthetic
Aα motor
0.8–1.4 mm
Aδ sensory
0.3–0.7 mm
C sensory and postganglionic

Fig. 27.5

► **Diffusion and effect.** During diffusion from the injection site (i.e., the interstitial space of connective tissue) to the axon of a sensory nerve, the local anesthetic must traverse the **perineurium.** The multilayered perineurium is formed by connective tissue cells linked by *zonulae occludentes* (p. 38) and therefore constitutes a closed lipophilic barrier.

Local anesthetics in clinical use are usually tertiary amines; at the pH of interstitial fluid these exist partly as the neutral lipophilic base (symbolized by particles marked with two red dots) and partly as the protonated form, i.e., amphiphilic cation (symbolized by particles marked with one blue and one red dot). The uncharged form can penetrate the perineurium and enters the **endoneural space,** where a fraction of the drug molecules regains a positive charge in keeping with the local pH. The same process repeats itself when the drug penetrates through the axonal membrane (axolemma) into the **axoplasm** from which it exerts its action on the sodium channel; and again when it diffuses out of the endoneural space through the unfenestrated endothelium of capillaries into the blood.

The concentration of local anesthetic at the site of action is, therefore, determined by the speed of penetration into the endoneurium and axoplasm and the speed of diffusion into the capillary blood. To enable a sufficiently fast build-up of drug concentration at the site of action, there must be a correspondingly large concentration gradient between drug depot in the connective tissue and the endoneural space. Injection of solutions of low concentration will fail to produce an effect; however, too high concentrations must also be avoided because of the danger of intoxication resulting from too rapid systemic absorption into the blood.

To ensure a reasonably long-lasting local effect with minimal systemic action, a **vasoconstrictor** (epinephrine, less frequently norepinephrine or vasopressin derivatives) is often co-administered in an attempt to confine the drug to its site of action. As blood flow is diminished, diffusion from the endoneural space into the capillary blood decreases. Addition of a vasoconstrictor, moreover, helps to create a relative ischemia in the surgical field. Potential disadvantages of catecholamine-type vasoconstrictors include the reactive hyperemia following washout of the constrictor agent and cardiostimulation when epinephrine enters the systemic circulation. In lieu of epinephrine, the vasopressin analogue felypressin can be used as adjunctive vasoconstrictor (less pronounced reactive hyperemia, no arrhythmogenic action, but danger of coronary constriction). Vasoconstrictors must not be applied in local anesthesia involving the appendages (e.g., fingers, toes).

► **Characteristics of chemical structure.** Local anesthetics possess a uniform structure (p. 208). Generally they are secondary or tertiary amines. The nitrogen is linked through an intermediary chain to a lipophilic moiety—most often an aromatic ring system.

The amine function means that local anesthetics exist either as the neutral amine or as the positively charged ammonium cation, depending upon their dissociation constant (pK_a value) and the actual pH value. The pK_a of typical local anesthetics lies between 7.5 and 9. In its protonated form, the molecule possesses both a polar hydrophilic moiety (protonated nitrogen) and an apolar lipophilic moiety (ring system)—it is *amphiphilic.*

A. Disposition of local anesthetics in peripheral nerve tissue

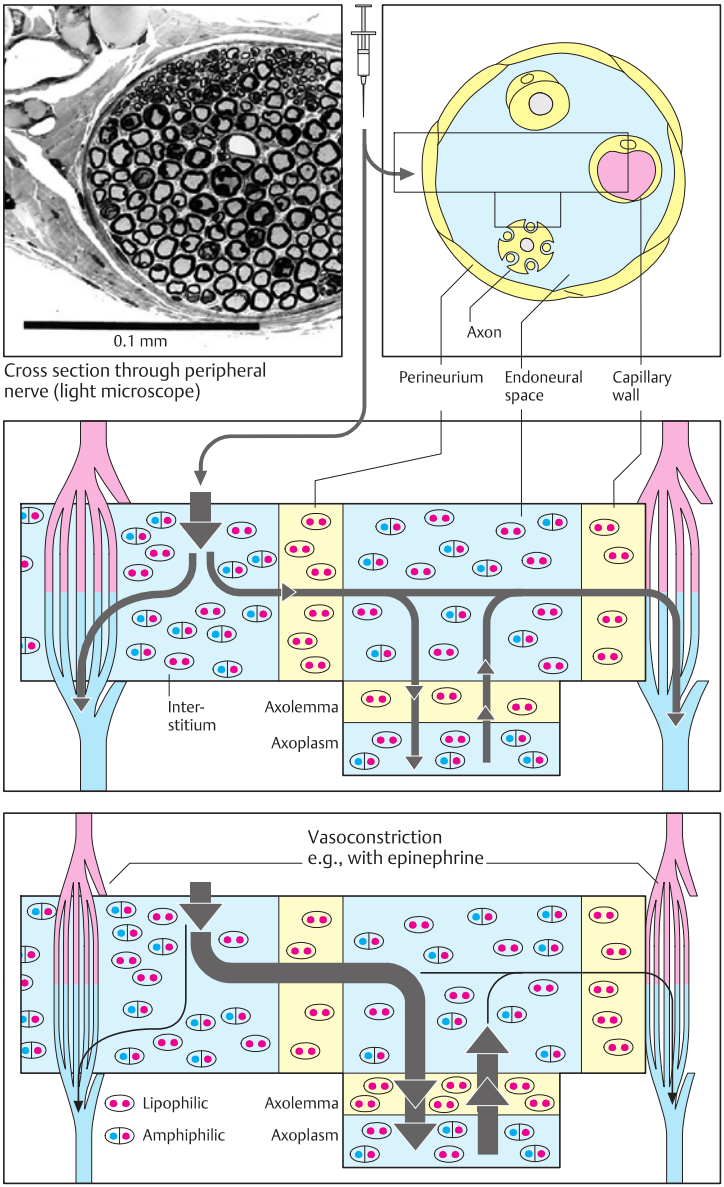


Fig. 27.6

Depending on the pK_a, from 50% to 5% of the drug may be present at physiological pH in the uncharged lipophilic form. This fraction is important because it represents the lipid membrane-permeable form of the local anesthetic (p. 42), which must take on its cationic amphiphilic form in order to exert its action. Clinically used local anesthetics are either esters or amides. Ester-type local anesthetics are subject to inactivation by tissue esterases. This is advantageous because of the diminished danger of systemic intoxication. On the other hand, the high rate of bioinactivation and, therefore, shortened duration of action is a disadvantage.

Procaine cannot be used as surface anesthetic because it is inactivated faster than it can penetrate the dermis or mucosa. Chloroprocaine, a derivative, is used for spinal anesthesia.

Lidocaine is broken down primarily in the liver by oxidative N-dealkylation. It is an effective local anesthetic in 0.25–1% solution. 5% ointments are required for topical anesthesia. Lidocaine is also used as an antiarrhythmic agent.

In *mepivacaine*, the nitrogen atom usually located at the end of the side chain forms part of a cyclohexane ring.

Degradation can occur only to a restricted extent in *prilocaine* and *carticaine* because both carry a substituent on the C-atom adjacent to the nitrogen group. Carticaine possesses a carboxymethyl group on its thiophene ring. At this position, ester cleavage can occur, resulting in the formation of a polar $-COO^-$ group, loss of the amphiphilic character, and conversion to an inactive metabolite.

Ropivacaine is the S-enantiomer of a *bupivacaine* derivative. It has a very long duration of action (many hours) and is highly suitable for epidural and spinal anesthesia.

Benzocaine is a member of the group of local anesthetics lacking a nitrogen atom that can be protonated at physiological pH. It is used exclusively as a surface anesthetic.

Another agent used for surface anesthesia is the uncharged polidocanol (macrogol lauryl ether, lauromacrogol), which has the formula

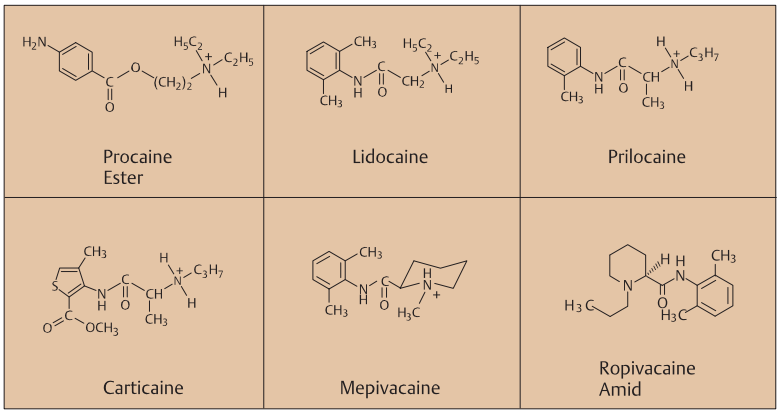
$$H_3C-(CH_2)_{11}-(O-CH_2-CH_2)_9-OH \qquad (27.1)$$

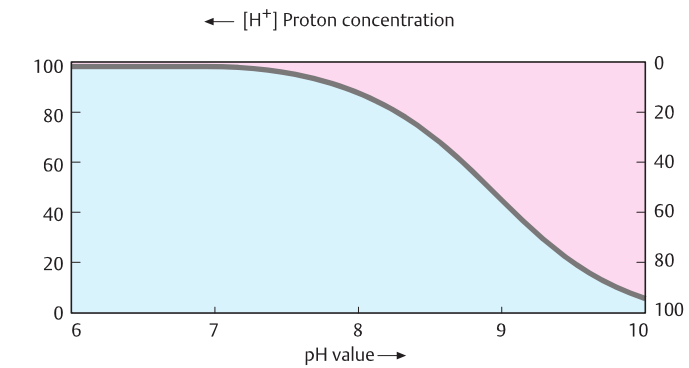
consisting of a hydrophobic and a hydrophilic part. At higher concentrations, polidocanol is toxic and is used for obliteration (e.g. of esophageal varices in hepatic cirrhosis).

► **Adverse effects of local anesthetics (LAs).** The cellular point of attack of LAs is a "fast" Na^+ channel, opening of which initiates the action potential. LAs block this channel. Fast sodium channels also operate in other excitable tissues including nerve cells of the brain and muscle or specialized conducting tissues of the heart. The action of LAs is thus not confined to nerve tissue; it is not organ-specific. Accordingly, serious adverse effects occur when LAs enter the circulation too rapidly or in too high concentrations. In the heart, impulse conduction is disrupted, as evidenced by atrioventricular block or, at worst, ventricular arrest. In the CNS, different regions are perturbed with a resultant loss of consciousness and development of seizures. Since no specific LA antidote is available, symptomatic countermeasures need to be taken immediately. If signs of cardiac inhibition predominate, epinephrine must be given intravenously. If CNS toxicity is present, anticonvulsant drugs have to be administered (e.g., diazepam i.v.).

Ziconotide is a new antinociceptive agent for local administration. It is a synthetically produced analogue of conotoxin, which is used by marine cone snails to paralyze their prey. The effect is due to blockade of neuronal N-type calcium channels. For severe chronic pain, ziconotide can be delivered through an intrathecal catheter to the spinal cord, where it blocks impulse transmission in the posterior horn. Ziconotide is not well tolerated (CNS side effects) but it is helpful in some cases as a last resort.

A. Local anesthetics and pH value





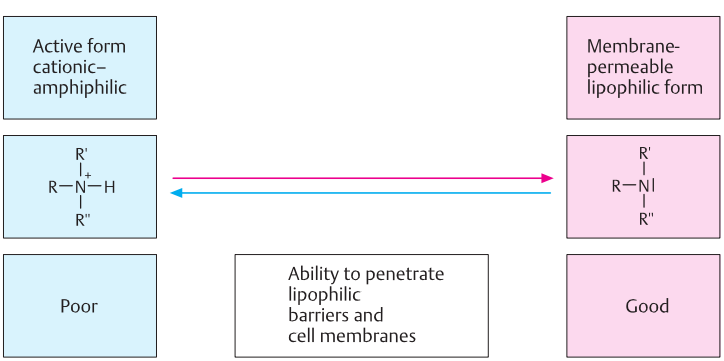


Fig. 27.7

Opioids = Opiates

There are binding sites on nerve cells for endogenous substances known as **endogenous opioids.** Opioid receptors are present in various areas of the brain, in the spinal cord, and in the nerve plexuses of the intestine and bladder. There are different types of receptors, which are designated by the Greek letters δ, k, and μ. Endogenous opioids are peptides of varying length, which are cleaved from the precursors proenkephalin, pro-opiomelanocortin, and prodynorphin. All contain the amino acid sequence of the pentapeptides [met-] or [leu-] enkephalin: Tyr-Gly-Gly-Phe-Leu (or -Met). This is the active region that binds to the opioid receptors, increases K^+ conductivity, and thus produces hyperpolarization. This reduces the excitability of the cell.

The juice of the opium poppy *(Papaver somniferum)* contains a number of alkaloids. Dried opium juice is called opium and has been familiar since antiquity. The main alkaloid, **morphine,** was isolated in 1807. Apart from morphine, opium contains two other alkaloids of medical interest: codeine, an antitussive and weak analgesic, and papaverine, a spasmolytic. Morphine is a strong analgesic but has a narrow therapeutic index. It is not surprising that successors were sought that would have fewer side effects while preserving analgesic efficacy. There are a few semisynthetic morphine derivatives (e.g., hydromorphone, oxycodone, and buprenorphine) and a number of wholly synthetic drugs (e.g., meperidine, methadone, pentazocine, fentanyl). None of these drugs has any advantage over morphine in principle.

► **Opioid side effects.** The opioids inhibit the **respiratory center.** Even at therapeutic dosage, reduced responsiveness to the oxygen tension and CO_2 content in the blood can be detected. The respiratory center is particularly sensitive in the neonate, so if possible opiates should not be given to women during delivery. If the neonate actually has opioid-induced respiratory depression, this can be abolished immediately by giving naloxone. In adults with chronic **gas exchange disorder** (e.g., pulmonary emphysema), the respiratory center is hypersensitive to morphine and its derivatives. Even a normal dose can lead to central respiratory depression. The opiates are therefore contraindicated in patients with gas exchange disorders.

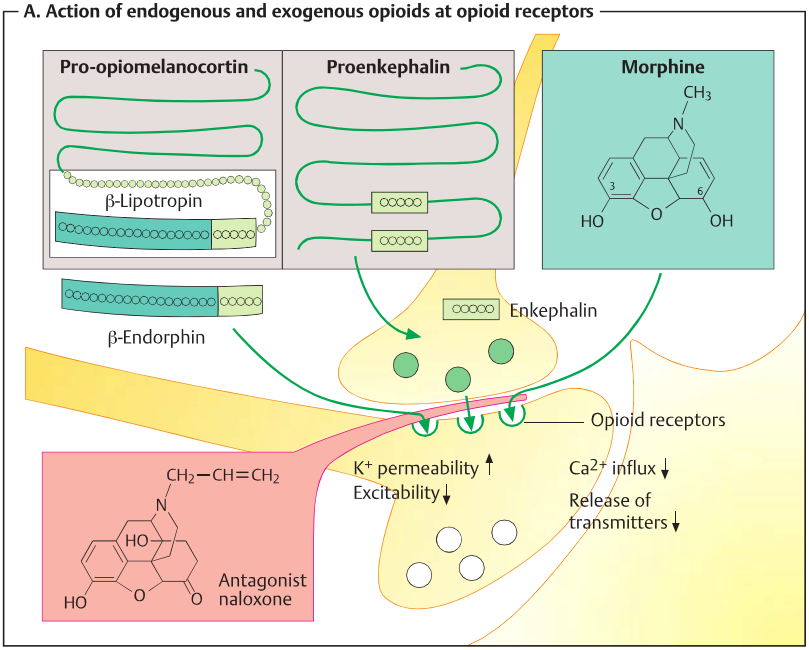
When used for the first time, opioids can **cause vomiting;** this effect is caused by stimulation of chemoreceptors in the area postrema. This side effect disappears with regular use.

The opioids stimulate **parasympathetic nuclei,** so miosis occurs regularly. This is important diagnostically as the pupils dilate only in the terminal stage of respiratory depression.

In the **intestinal tract,** smooth muscle tone is increased and propulsive motor activity is inhibited, resulting in constipation. Gastric emptying is delayed and drainage of bile and pancreatic secretion is hindered. Bladder voiding is also more difficult.

► **Tolerance.** With repeated administration of opiates, habituation to the central effects can occur. Higher doses are needed constantly in order to achieve similarly effective pain relief. The peripheral effects are less affected by this development of tolerance. Morphine-induced constipation can become so severe that opioid use has to be discontinued. Laxatives must often be prescribed from the start.

► **Opioid addiction.** Apart from the possibility of producing an increase in somatic tolerance, the opioids also have the "fatal" property of inducing **addiction.** The addiction is due to the euphoria they induce, which progresses to negative withdrawal symptoms as the effect of the drug wears off. "Opiate hunger" develops. The intensity of the "morphine high" when the opioid takes effect is determined by a kinetic parameter: the faster the opioid concentration increases in the extracellular space of the brain, the greater is the "kick" that the addict experiences. It is therefore the increase in concentration that forms the basis for the development of addiction. The "addiction potential" of the individual opioids depends on (a) their lipophilicity (fast penetration of the blood–brain barrier) and (b) the drug formulation (e.g., delayed-release forms). ► Fig. 27.10**C** shows the estimated risk of developing addiction depending on the drug property and route of administration.


A. Action of endogenous and exogenous opioids at opioid receptors
Pro-opiomelanocortin
β-Lipotropin
Proenkephalin
Morphine
CH3
N
HO
O
OH
3
6
β-Endorphin
Enkephalin
Opioid receptors
K+ permeability
Excitability
Ca2+ influx
Release of transmitters
CH2—CH=CH2
Antagonist naloxone

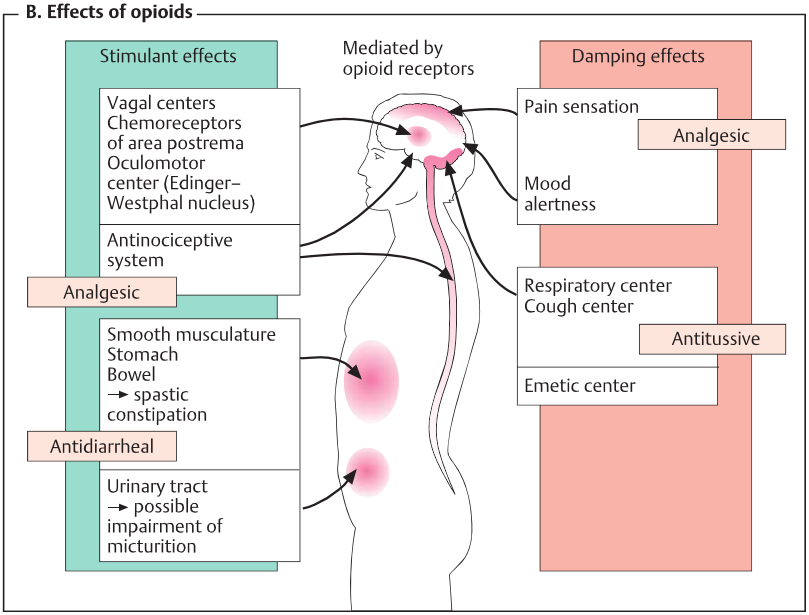

B. Effects of opioids
Stimulant effects
Mediated by opioid receptors
Damping effects
Vagal centers
Chemoreceptors of area postrema
Oculomotor center (Edinger–Westphal nucleus)
Antinociceptive system
Analgesic
Smooth musculature
Stomach
Bowel
→ spastic constipation
Antidiarrheal
Urinary tract
→ possible impairment of micturition
Pain sensation
Analgesic
Mood
alertness
Respiratory center
Cough center
Antitussive
Emetic center

Fig. 27.8

Prescription of most opioids is subject to special regulations (controlled drug legislation). Certain opioid analgesics such as codeine and tramadol can be prescribed in the ordinary way as they involve a lower risk of developing dependence.

► **Indication for opioids.** In practice, opioids are used in the following situations. (a) Sudden, highly acute pain; **morphine** can be given subcutaneously, but this should be limited to a short period. (b) Chronic pain, especially when it occurs in terminal conditions. In this situation, patients can be prescribed **controlled-release morphine tablets** or **fentanyl patches** generously. It is important to achieve steady blood levels. The patients should themselves regulate their morphine tablet use according to their needs. (c) If the pain is not severe enough to warrant a full-strength opiate, **tramadol** (see below) may be employed. This is intermediate between opioids and antipyretic analgesics, and does not have a potential for dependence.

Two morphine **derivatives** with substituents on the –OH groups require separate description. These are (1) **heroin** and (2) the metabolite **morphine-6-glucuronide.**

(**1**) **Heroin** is not present in opium. In heroin, the two –OH groups of morphine are esterified with acetic acid. Masking of morphine's –OH groups by esterification with acetic acid confers lipophilic properties on heroin so that it penetrates lipid barriers readily. After intravenous injection, heroin passes the blood–brain barrier unhindered to reach the CNS, the CSF concentration rises rapidly, and there is a pronounced "high." The analgesic effect is comparatively weak. It must be stated clearly that **heroin is not a medication** but is used only as a drug of abuse after synthetic manufacture. Heroin addiction is a serious medical problem: the addict decays physically, breaks down mentally, and comes into conflict with the law. Withdrawal treatment programs are only moderately successful despite great expense.

When the opioid addict's drug supply is interrupted, **withdrawal symptoms** develop and can last for many days. After the acute withdrawal symptoms have subsided, the morphine addiction is still by no means cured. Opiate hunger persists for a long time.

Withdrawal treatment must take place in a closed facility. It requires central depressant drugs in addition to psychotherapeutic care. The chances of success can be regarded as only moderate. A "popular" measure for removing heroin addicts from their illegal environment consists of giving oral **methadone.** This replacement does not produce an opioid high (it accumulates too slowly; see ► Fig. 27.10**C**), it only prevents withdrawal symptoms while the addiction continues. Some addicts on methadone treatment still want the heroin high so much that they inject heroin again in addition to taking methadone. This rash behavior can be fatal because the inhibitory effect of the two opiates on the respiratory center is additive, producing central respiratory depression. Some have demanded that heroin be classified as a medication that is given to addicts as a daily injection. The addiction is maintained. Heroin is then sometimes renamed **diamorphine** (short for diacetylmorphine, which was already its chemical name).

(**2**) Morphine is altered metabolically by glucuronidation in the 3 and 6 positions. The 3-glucuronide predominates quantitatively and is ineffective as an analgesic. In contrast, **morphine-6-glucuronide** is more highly analgesic than the parent drug. The strange thing is that the 6-glucuronide is highly hydrophilic and is actually unable to pass the blood–brain barrier. However, there is evidence that an anion transport polypeptide in the vascular endothelium of cerebral vessels (► Fig. 27.10**B**) enables it to pass this barrier. When the concentrations of morphine and the 6-glucuronide are measured in a volume unit of brain tissue following a morphine dose, more morphine than morphine-6-glucuronide is found. However, the analgesic effect can be attributed to the 6-glucuronide; this substance cannot penetrate into the brain cells because of its hydrophilicity and so remains extracellular. In contrast, morphine penetrates into the cells, which have a much greater volume. The morphine concentration in the extracellular fluid therefore falls to very low levels. The opioid receptor is located on the surface of nerve cells and is only reached from outside. Intracellular morphine is unable to react with a receptor and so is unable to participate in the analgesic effect.

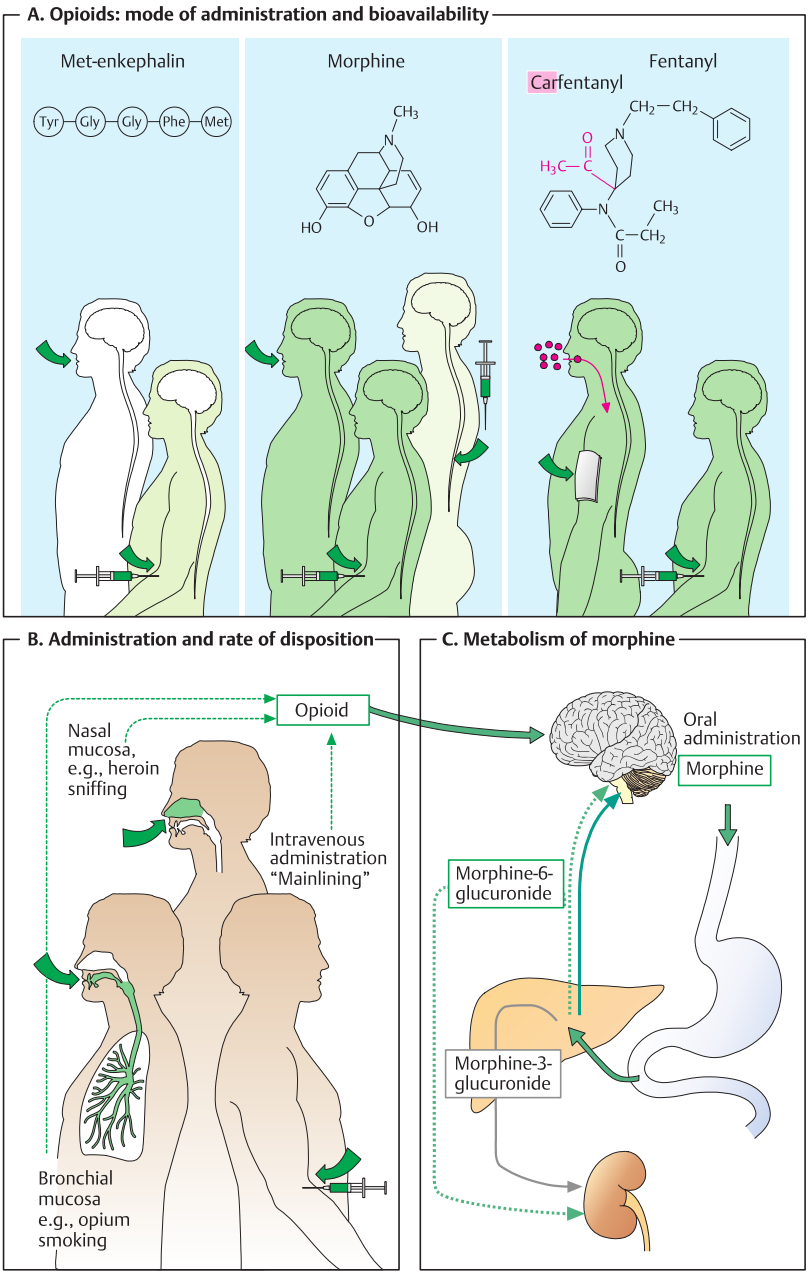

A. Opioids: mode of administration and bioavailability
Met-enkephalin
Tyr
Gly
Gly
Phe
Met
Morphine
CH3
N
HO
O
OH
Fentanyl
Carfentanyl
CH2—CH2
O
H3C—C
N
N
CH3
C—CH2
O
B. Administration and rate of disposition
Opioid
Nasal mucosa, e.g., heroin sniffing
Intravenous administration "Mainlining"
Bronchial mucosa e.g., opium smoking
C. Metabolism of morphine
Oral administration
Morphine
Morphine-6-glucuronide
Morphine-3-glucuronide

Fig. 27.9

► **Special opioids. Antagonists.** A few substances from the opioid group deserve special mention. **Naloxone** is a pure antagonist at the opioid receptors with a life-saving action in opioid intoxication. Chemically this antagonist differs only slightly from morphine; instead of the methyl group on the nitrogen, the substituent in this case is $-CH_2-CH=CH_2$. Naloxone is suitable for parenteral administration only because of high presystemic elimination after oral intake. **Naltrexone** is more stable metabolically and is used orally. Naltrexone can be used to support withdrawal therapy. As a result of methylation, **methylnaltrexone** has a permanently positively charged quaternary nitrogen. It can be used to counter constipation in patients treated with opioids without abolishing the analgesic effect of the opioid; when given by injection it reaches the gut via the bloodstream but is unable to overcome the blood–brain barrier on account of its sustained electrical charge.

► **Agonist/antagonist opioids.** **Nalbuphine** is an antagonist at the opioid receptor μ subtype and an agonist at the k-subtype. It is not classified as a controlled drug for prescribing purposes and is given by injection.

► **Opioid agonists that increase the action of biogenic amines.** **Tramadol** has no addiction potential but its analgesic action is weaker than that of morphine. The mechanism of the analgesic action is complex and involves more than the action on opioid receptors. Tramadol is a racemate. The (+) enantiomer has greater affinity for the μ-receptor and is more effective in this respect than the (–) enantiomer. In addition, the transport systems for neuronal reuptake of norepinephrine and serotonin are inhibited with reversal of the enantioselectivity (► Fig. 27.10**C**). The main side effect is vomiting (~10% of cases). However, it is useful in many cases and is not subject to controlled-drug prescribing regulations. *Tapentadol* resembles tramadol in that it has an inhibitory effect on neuronal reuptake, but only that of norepinephrine, in addition to opioid receptor activation. Tapentadol is subject to controlled-drug prescribing regulations.

► **Agonists.** **Fentanyl,** which has a particularly high affinity for opioid receptors, merits special interest. It is about 20 times more potent than morphine. Because of its good penetration, it can be used in patch form. This results in very steady drug levels with low addiction potential. Fentanyl-like substances such as alfentanil and sufentanil are given intravenously during operations. Remifentanil differs from these by its rapid ester cleavage. An incredible reinforcement of the effect is achieved by a small substituent (see the red structure in ► Fig. 27.9**A**); carfentanyl has 5000 times the efficacy of morphine. The substance can be sprayed as a fine aerosol and when inhaled it has a narcotic/anesthetic and respiratory center depressant action. In the USA it is in use as a veterinary drug to tame/control large wild animals.

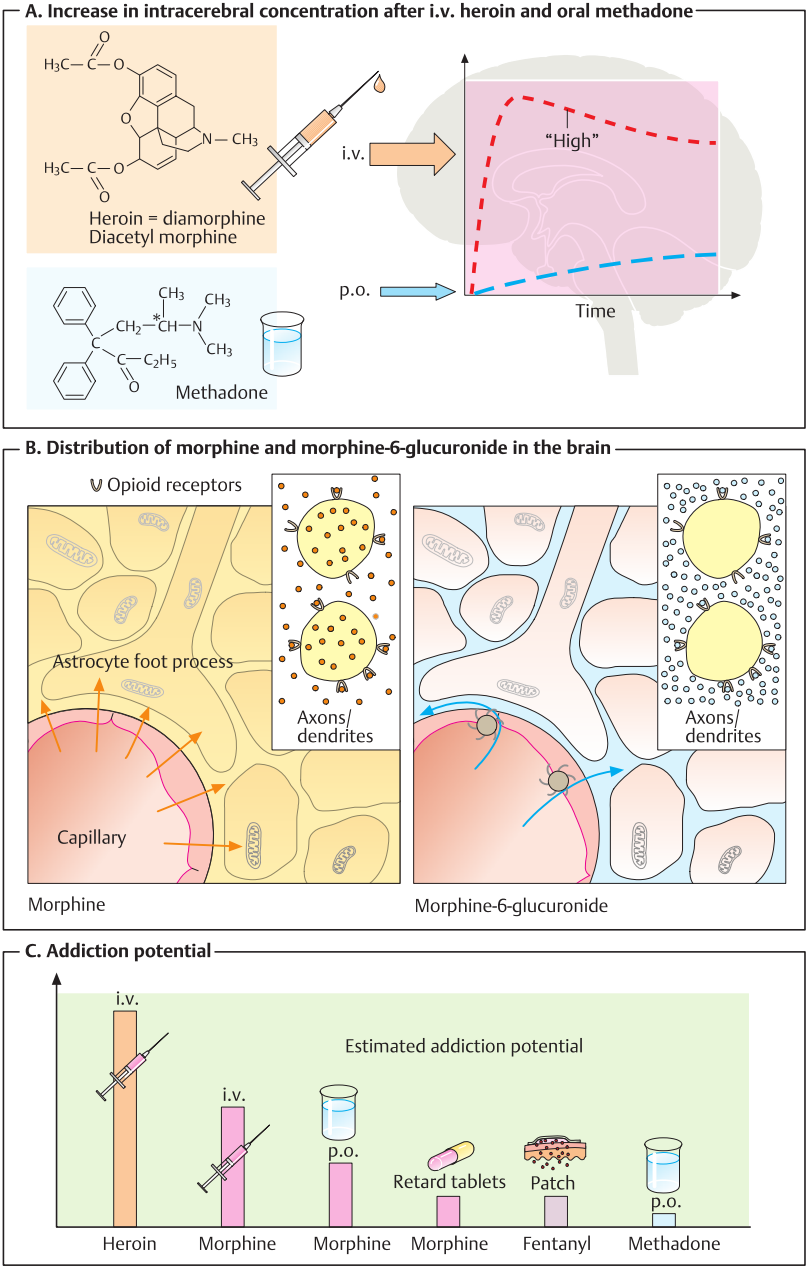

A. Increase in intracerebral concentration after i.v. heroin and oral methadone
Heroin = diamorphine
Diacetyl morphine
Methadone
i.v.
p.o.
"High"
Time
B. Distribution of morphine and morphine-6-glucuronide in the brain
Opioid receptors
Astrocyte foot process
Axons/
dendrites
Capillary
Morphine
Morphine-6-glucuronide
C. Addiction potential
Estimated addiction potential
i.v.
i.v.
p.o.
Retard tablets
Patch
p.o.
Heroin
Morphine
Morphine
Morphine
Fentanyl
Methadone

Fig. 27.10

General Anesthesia and General Anesthetic Drugs

Anesthesia became part of medical practice in the middle of the 19th century. Painful operations became possible as consciousness and pain perception could be switched off reversibly. Anesthesia was one of the major advances in medicine in the 19th century.

General anesthesia is a state of drug-induced reversible inhibition of central nervous function, during which surgical procedures can be carried out in the absence of consciousness, responsiveness to pain, defensive or involuntary movements, and significant autonomic reflex responses (▶ Fig. 28.1**A**).

The required level of anesthesia depends on the intensity of the pain-producing stimuli, i.e., the degree of nociceptive stimulation. The skillful anesthetist, therefore, dynamically adapts the plane of anesthesia to the demands of the surgical situation. Originally, anesthesia was achieved with a single anesthetic agent (e.g., diethyl ether, first successfully demonstrated in 1846 by W. T. G. Morton, Boston). To suppress defensive reflexes, such a "mono-anesthesia" necessitates a dosage in excess of that needed to cause unconsciousness, thereby increasing the risk of paralyzing vital functions, such as cardiovascular homeostasis (▶ Fig. 28.1**B**). Modern anesthesia employs a combination of different drugs to achieve the goals of surgical anesthesia (**balanced anesthesia**). This approach reduces the hazards of anesthesia. Examples of drugs that are used concurrently or sequentially as anesthesia adjuncts are listed in ▶ Fig. 28.1**C**. Neuromuscular blocking agents are covered elsewhere in more detail (p. 192). Recall that "curarization" of the patient necessitates artificial ventilation. However, the use of neuromuscular blockers is making an essential contribution to risk reduction in modern anesthesia. In the following, some special methods of anesthesia are considered before presentation of the anesthetic agents.

Neuroleptanalgesia can be considered a special form of combination anesthesia: the short-acting opioid analgesic *fentanyl* is combined with a strongly sedating and affect-blunting neuroleptic. Because of major drawbacks, including insufficient elimination of consciousness and extrapyramidal motor disturbances, this procedure has become obsolete.

In **regional anesthesia** (spinal anesthesia) with a local anesthetic (p. 204), nociceptive conduction is interrupted. Since consciousness is preserved, this procedure does not fall under the definition of anesthesia.

According to their mode of administration, **general anesthetics** in the narrow sense are divided into inhalational (gaseous, volatile) and injectable agents.

Inhalational anesthetics (p. 218) are administered in and, for the most part, eliminated via respired air. They serve especially to maintain anesthesia.

Injectable anesthetics (p. 220) are frequently employed for induction. Intravenous injection and rapid onset of action are clearly more agreeable to the patient than is breathing a stupefying gas. The effect of most injectable anesthetics is limited to a few minutes. This allows brief procedures to be carried out or preparation of the patient for inhalational anesthesia (intubation). Administration of the volatile anesthetic must then be titrated in such a manner as to counterbalance the waning effect of the injectable agent. Increasing use is now being made of injectable, instead of inhalational, anesthetics during prolonged combined anesthesia (e.g., propofol; total intravenous anesthesia—TIVA).

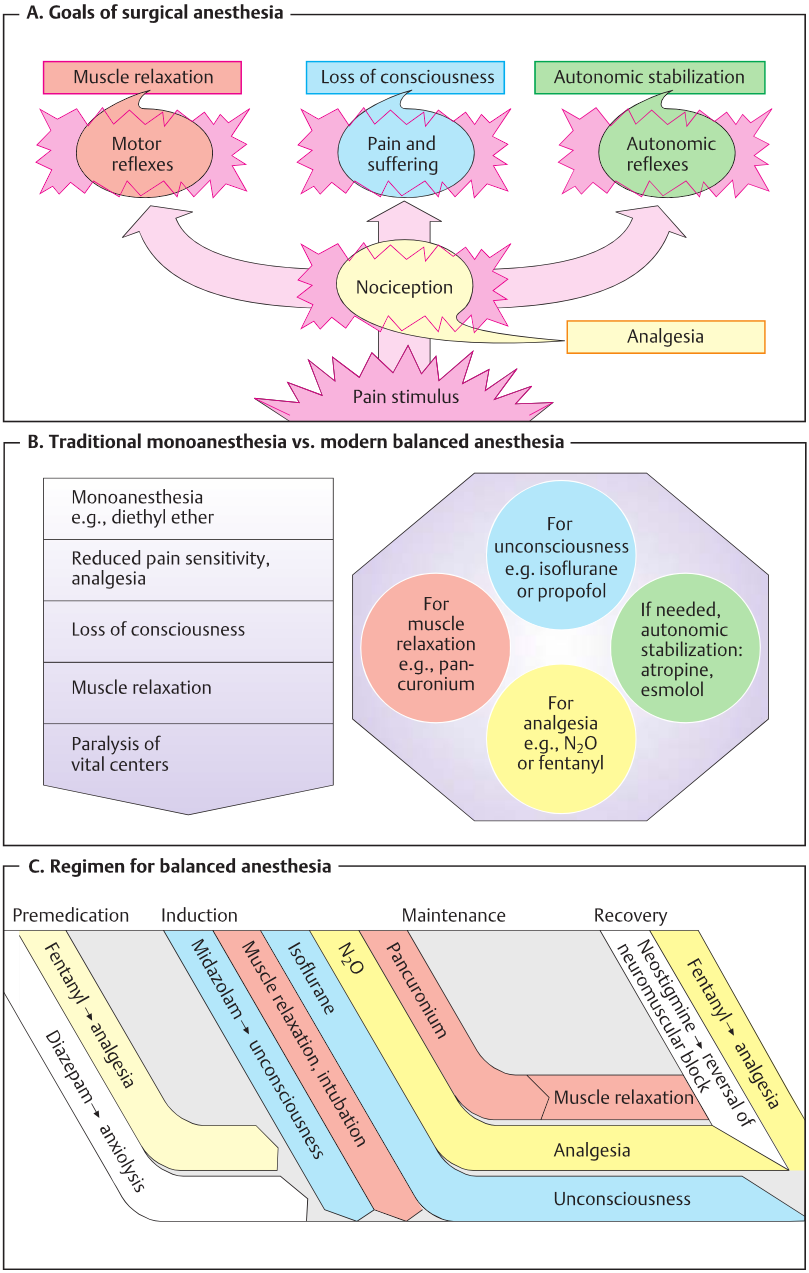

A. Goals of surgical anesthesia
Muscle relaxation
Loss of consciousness
Autonomic stabilization
Motor reflexes
Pain and suffering
Autonomic reflexes
Nociception
Analgesia
Pain stimulus
B. Traditional monoanesthesia vs. modern balanced anesthesia
Monoanesthesia e.g., diethyl ether
Reduced pain sensitivity, analgesia
Loss of consciousness
Muscle relaxation
Paralysis of vital centers
For unconsciousness e.g. isoflurane or propofol
For muscle relaxation e.g., pancuronium
If needed, autonomic stabilization: atropine, esmolol
For analgesia e.g., N_2O or fentanyl
C. Regimen for balanced anesthesia
Premedication
Induction
Maintenance
Recovery
Fentanyl → analgesia
Diazepam → anxiolysis
Midazolam → unconsciousness
Muscle relaxation, intubation
Isoflurane
N_2O
Pancuronium
Muscle relaxation
Analgesia
Unconsciousness
Neostigmine → reversal of neuromuscular block
Fentanyl → analgesia

Fig. 28.1

Inhalational Anesthetics

The mechanism of action of inhalational anesthetics is not known in detail. In the first instance, the diversity of chemical structures (the inert gas xenon; hydrocarbons; halogenated hydrocarbons) possessing anesthetic activity appeared to argue against the involvement of specific sites of action. The *correlation between anesthetic potency and lipophilicity* of anesthetic drugs (▶ Fig. 28.2**A**) pointed to a nonspecific uptake into the hydrophobic interior of the plasmalemma, with a resultant impairment of neuronal function. Meanwhile, several lines of evidence support an interaction with membrane proteins; among these ligand-gated ion channel proteins assume special importance. Experimental studies favor the idea that anesthetics enhance the effectiveness of inhibitory GABA and glycine receptors, while attenuating responsiveness to stimulation of excitatory glutamate receptors.

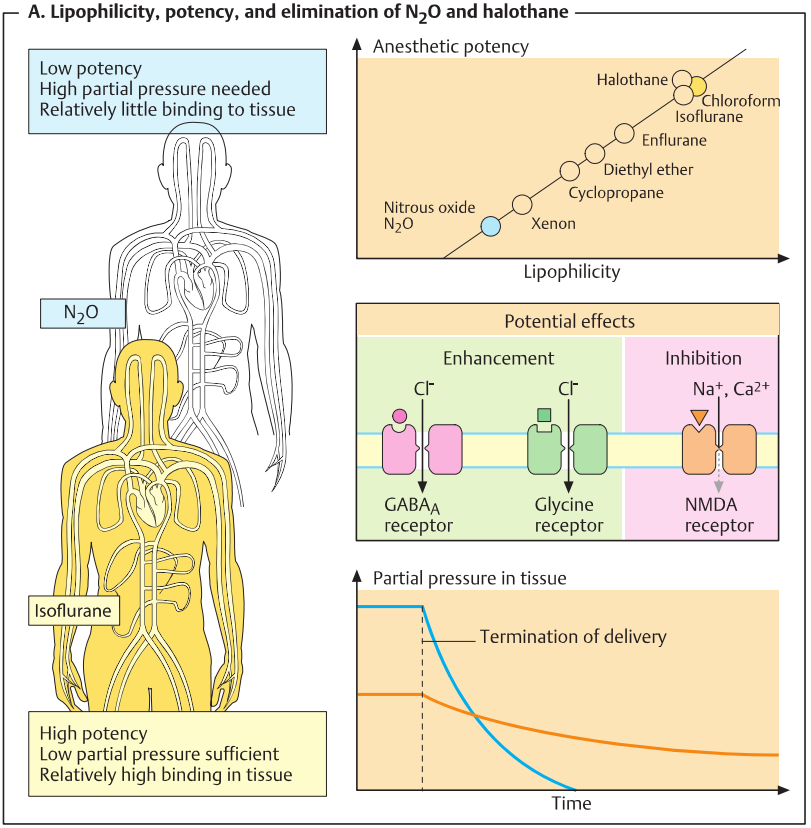
Anesthetic potency can be expressed in terms of the minimal alveolar concentration (MAC) at which 50% of patients remain immobile following a defined painful stimulus (skin incision). Whereas the poorly lipophilic nitrous oxide must be inhaled in high concentrations, much smaller concentrations are required in the case of the more lipophilic halothane.

The **rates of onset and cessation** of action vary widely among different inhalational anesthetics and also depend on the degree of lipophilicity. In the case of nitrous oxide, elimination from the body is rapid when the patient is ventilated with normal air. Owing to the high partial pressure in blood, the driving force for transfer of the drug into expired air is large and, since tissue uptake is minor, the body can be quickly cleared of nitrous oxide. In contrast, with halothane, partial pressure in blood is low and tissue uptake is high, resulting in a much slower elimination.

Given alone, *nitrous oxide* (N_2O, dinitrogen monoxide, "laughing gas") is incapable of producing anesthesia of sufficient depth for surgery, even when taking up 70% of the inspired air volume (30 vol. % O_2 is necessary!). It has good analgesic efficacy that can be exploited when it is used in conjunction with other anesthetics. As a gas, N_2O can be administered directly; it is exhaled unaltered and in full (▶ Fig. 28.2**B**).

Halogenated hydrocarbons have proven to be particularly useful inhalational anesthetics. **Halothane** was the first compound to be used widely; it has good anesthetic properties (rapid uptake and excretion) but also causes serious side effects. It is converted in the liver to toxic metabolites, which give rise to hepatic dysfunction. Halothane also reduces blood pressure and has a negative inotropic effect. The development of other substances in this group that are largely metabolically stable was a major advance. **Isoflurane** is an anesthetic that differs positively from halothane. It is a halogenated methyl ethyl ether (F_3C-HCCl-O-HCF_2) that is practically inert metabolically. Uptake and excretion are very fast. At appropriate dosage there is no interference with cardiovascular function. **Desflurane** and **sevoflurane,** two analogue products, are now on the market; these have the positive properties of isoflurane.

Halothane is no longer on the market. Two other inhalational anesthetics have also been withdrawn: methoxyflurane because of its metabolic instability and enflurane because it lowered the seizure threshold.


A. Lipophilicity, potency, and elimination of N_2O and halothane
Low potency
High partial pressure needed
Relatively little binding to tissue
N_2O
Isoflurane
High potency
Low partial pressure sufficient
Relatively high binding in tissue
Anesthetic potency
Halothane
Chloroform
Isoflurane
Enflurane
Diethyl ether
Cyclopropane
Nitrous oxide N_2O
Xenon
Lipophilicity
Potential effects
Enhancement
Inhibition
Cl^-
Cl^-
Na^+, Ca^{2+}
$GABA_A$ receptor
Glycine receptor
NMDA receptor
Partial pressure in tissue
Termination of delivery
Time

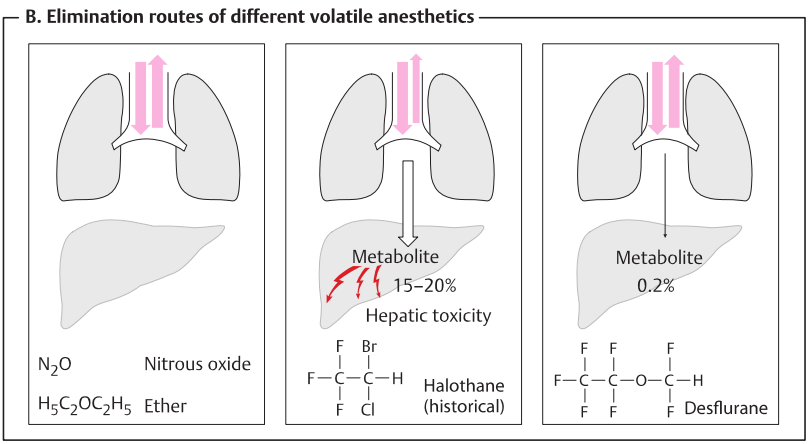

B. Elimination routes of different volatile anesthetics
N_2O Nitrous oxide
$H_5C_2OC_2H_5$ Ether
Metabolite
15–20%
Hepatic toxicity
Halothane (historical)
Metabolite
0.2%
Desflurane

Fig. 28.2

Injectable Anesthetics

Substances from different chemical classes suspend consciousness when given intravenously and can be used as injectable anesthetics (▶ Fig. 28.3**A**). Like inhalational agents, most of these drugs affect consciousness only and are devoid of analgesic activity (exception: ketamine). The effect appears to arise from an interaction with ligand-gated ion channels. Channels mediating neuronal excitation (NMDA receptor, see below) are blocked, while the function of channels damping excitation, e.g., the $GABA_A$ receptor (p. 222); and, for three drugs, additionally also the glycine receptor) is enhanced allosterically.

Most injectable anesthetics are characterized by a short duration of action. The rapid cessation of action is largely due to **redistribution:** after intravenous injection, brain concentration climbs rapidly to effective anesthetic levels because of the high cerebral blood flow; the drug then distributes evenly in the body, i.e., concentration rises in the periphery, but falls in the brain—redistribution and cessation of anesthesia (▶ Fig. 28.3**A**). Thus, the effect subsides before the drug has left the body. A second injection of the same drug would encounter "presaturated" body compartments and thus be difficult to predict in terms of effect intensity. Only etomidate and propofol may be given by infusion over a longer period to maintain unconsciousness. If no additional inhalational agent is employed, the procedure is referred to as *total intravenous anesthesia (TIVA).*

Thiopental and *methohexital* belong to the barbiturates, which, depending on dose, produce sedation, sleepiness, or anesthesia. Barbiturates lower pain threshold and thereby facilitate defensive reflex movements; they also depress central inspiratory drive. Barbiturates are frequently used for induction of anesthesia.

Ketamine has analgesic activity that persists up to 1 hour after injection, well beyond the initial period of unconsciousness (~15 minutes only). On regaining consciousness, the patient may experience a disconnection between outside reality and inner mental state *(dissociative anesthesia).* Frequently there is memory loss for the duration of the recovery period; however, adults in particular complain about distressing dreamlike experiences. These can be counteracted by administration of a benzodiazepine (e.g., midazolam). The CNS effects of ketamine arise, in part, from an interference with excitatory glutamatergic transmission via ligand-gated cation channels of the NMDA subtype, at which ketamine acts as a channel blocker. The nonnatural excitatory amino acid *N*-methyl D-aspartate (NMDA) is a selective agonist at this receptor. Ketamine can induce release of catecholamines with a resultant increase in heart rate and blood pressure.

Propofol has a remarkably simple structure resembling that of phenol disinfectants. Because the substance is water-insoluble, an injectable emulsion is prepared by means of soy oil, phosphatide, and glycerol. The effect has a rapid onset and decays quickly, being experienced by the patient as fairly pleasant. The intensity of the effect can be well controlled during prolonged administration. Possible adverse reactions include hypotension and respiratory depression, and a potentially fatal syndrome of bronchospasm, hypotension, and erythema.

The anesthetic effect of (+)-etomidate subsides within a few minutes owing to redistribution of the drug. Etomidate can provoke myoclonic movements that can be prevented by premedication with a benzodiazepine or an opioid. Because it has little effect on the autonomic nervous system, it is suitable for induction in combination anesthesia. Etomidate inhibits cortisol synthesis in subanesthetic doses and can therefore be used in the long-term treatment of adrenocortical overactivity (Cushing disease).

Midazolam is a rapidly metabolized benzodiazepine (p. 224) that is used for induction of anesthesia.

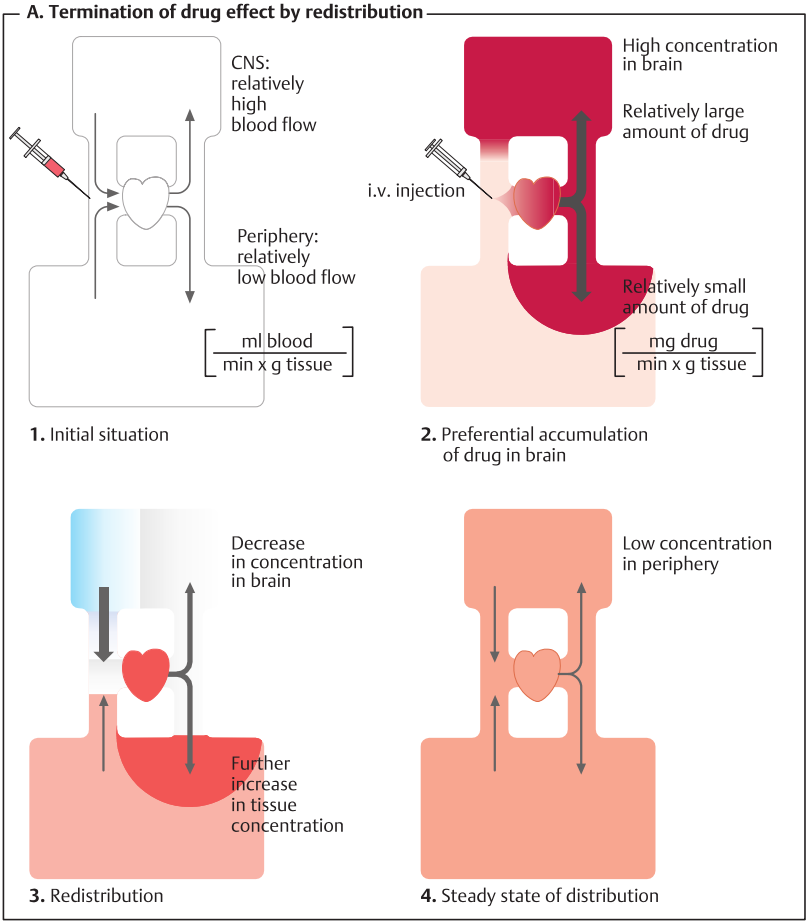

A. Termination of drug effect by redistribution
CNS:
relatively
high
blood flow
Periphery:
relatively
low blood flow
ml blood / min x g tissue
1. Initial situation
High concentration
in brain
Relatively large
amount of drug
i.v. injection
Relatively small
amount of drug
mg drug / min x g tissue
2. Preferential accumulation
of drug in brain
Decrease
in concentration
in brain
Further
increase
in tissue
concentration
3. Redistribution
Low concentration
in periphery
4. Steady state of distribution
B. Intravenous anesthetics
Sodium thiopental
Ketamine
NMDA receptor
blockade
Etomidate
Sodium methohexital
Propofol
Activation of glycine receptors
Midazolam
Activation of GABA receptors

Fig. 28.3

Benzodiazepines

Balanced CNS activity requires inhibitory and excitatory mechanisms. Spinal and cerebral inhibitory interneurons chiefly utilize γ-aminobutyric acid (GABA) as transmitter substance, which decreases the excitability of target cells via **$GABA_A$ receptors.** Binding of GABA to the receptor leads to opening of a chloride (Cl^-) ion channel, chloride influx, neuronal hyperpolarization, and decreased excitability. The pentameric subunit assembly making up the receptor/ion channel contains a high-affinity binding site for benzodiazepines, in addition to the GABA binding locus. Binding of benzodiazepine agonists allosterically enhances binding of GABA and its action on the channel. The prototypical benzodiazepine is diazepam. The "Z substances" such as zolpidem have the same action though they differ structurally; they are used only as hypnotics (see p. 344). Barbiturates also possess an allosteric binding site on the Cl^- channel protein; their effect is to increase the channel mean open-time during GABA stimulation.

Benzodiazepines exhibit a broad spectrum of activity: they exert sedating, sleep-inducing, anxiolytic, myorelaxant, and anticonvulsant effects and can be used for induction of anesthesia. Of special significance for the use of benzodiazepines is their wide margin of safety. At therapeutic dosages, neither central respiratory control nor cardiovascular regulation are affected. By virtue of these favorable properties, benzodiazepines have proved themselves for a variety of indications. At low dosage, they calm restless or agitated patients and allay anxiety, though without solving problems. Use of benzodiazepines as sleep remedies is widespread. Here, preference is given to substances that are completely eliminated during the night hours (tetracyclic compounds such as brotizolam and alprazolam). For longer-lasting anxiolytic therapy, compounds should be selected that are eliminated slowly and ensure a constant blood level (e.g., diazepam).

In psychosomatic reactions, benzodiazepines can exert an uncoupling effect. They are therefore of great value in hyperacute disease states (e.g., myocardial infarction, p. 328) or severe accidents. Status epilepticus is a necessary indication for parenteral administration (p. 336); however, benzodiazepines can also be used for the long-term treatment of certain forms of epilepsy, if necessary in combination with other anticonvulsants. Rapidly eliminated benzodiazepines are suitable for the intravenous induction of anesthesia.

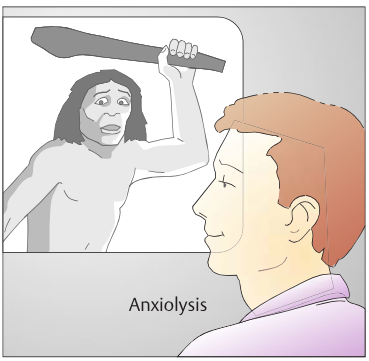
Prolonged use of benzodiazepines may lead to personality changes characterized by flattening of affect. Subjects behave with indifference and fail to react adequately. Any tasks requiring prompt and target-directed action—not only driving a motor vehicle—should be left undone when under the influence of benzodiazepines.

Benzodiazepine Antagonist

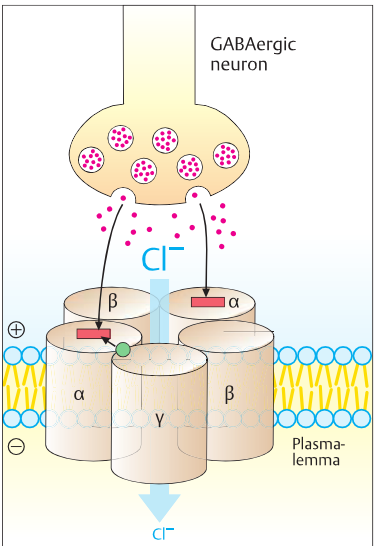
The drug **flumazenil** binds with high affinity to the benzodiazepine receptor but lacks any agonist activity. Consequently, the receptor is occupied and unavailable for binding of benzodiazepine agonists. Flumazenil is a specific antidote and is used with success for reversal of benzodiazepine toxicity or to terminate benzodiazepine sedation. When patients suffering from benzodiazepine dependence are given flumazenil, withdrawal symptoms are precipitated.

Flumazenil is eliminated relatively rapidly with a $t_{1/2}$ of ~1 hour. Therefore, the required dose of 0.2–1.0 mg i.v. must be repeated a corresponding number of times when toxicity is due to long-acting benzodiazepines.

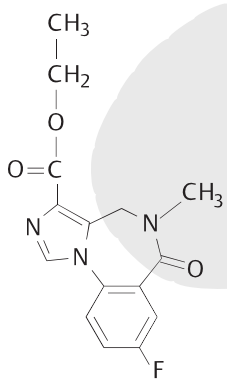
A. Action of benzodiazepines



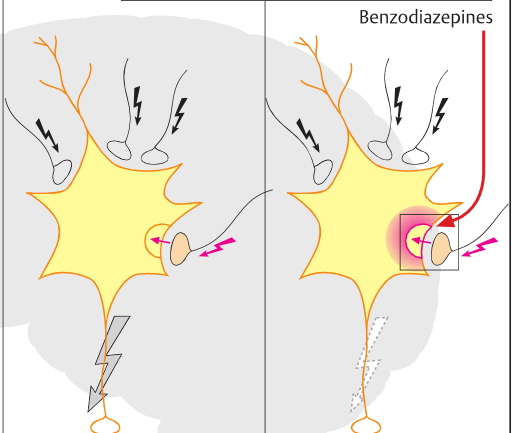
Plus anticonvulsant effect,
sedation, muscle relaxation



$GABA_A$-Receptor



Flumazenil
Benzodiazepine antagonist



Normal
GABAergic inhibition

Enhanced
GABAergic inhibition

Fig. 28.4

Pharmacokinetics of Benzodiazepines

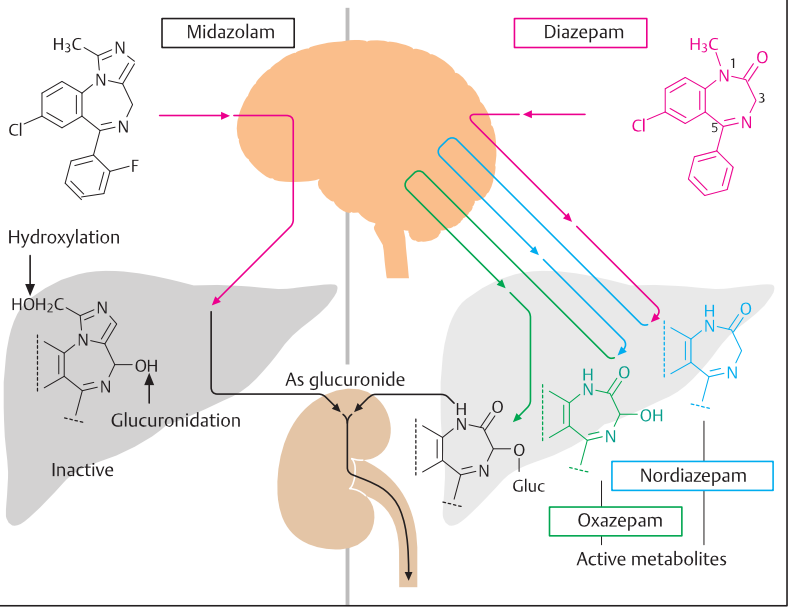
A typical metabolic pathway for benzodiazepines, as exemplified by the drug diazepam, is shown in ▶ Fig. 28.5**A**: first the methyl group on the nitrogen atom at position 1 is removed, with a concomitant or subsequent hydroxylation of the carbon at position 3. The resulting product is the drug oxazepam. These intermediary metabolites are biologically active. Only after the hydroxyl group (position 3) has been conjugated to glucuronic acid is the substance rendered inactive and, as a hydrophilic molecule, readily excreted renally. The metabolic degradation of desmethyldiazepam (nordiazepam) is the slowest step ($t_{1/2}$ = 30–100 hours). This sequence of metabolites encompasses other benzodiazepines that may be considered precursors of desmethyldiazepam, e.g., prazepam and chlordiazepoxide (the first benzodiazepine = Librium®). A similar metabolite pattern is seen in benzodiazepines in which an $-NO_2$ group replaces the chlorine atom on the phenyl ring and in which the phenyl substituent on carbon 5 carries a fluorine atom (e.g., flurazepam). With the exception of oxazepam, all these substances are long-acting. Oxazepam represents those benzodiazepines that are **inactivated in a single metabolic step;** nevertheless, its half-life is still as long as 8 ± 2 hours. Substances with a short half-life result only from introduction of an additional nitrogen-containing ring (▶ Fig. 28.5**A**) bearing a methyl group that can be rapidly hydroxylated. Midazolam, brotizolam, and triazolam are members of such tetracyclic benzodiazepines; the latter two are used as hypnotics, whereas midazolam given intravenously is employed for anesthesia induction.

Another possible way of obtaining compounds with an intermediate duration of action is to replace the chlorine atom in diazepam with an $-NO_2$ residue (rapidly reduced to an amine group with immediate acetylation) or with a bromine atom (which causes ring cleavage in the organism). In these cases, biological inactivation again consists of a one-step reaction.

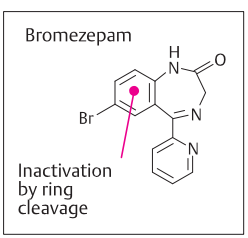
▶ **Dependence potential.** Prolonged regular use of benzodiazepines can lead to physical dependence. With the long-acting substances marketed initially, this problem was less obvious in comparison with other dependence-producing drugs, because of the delayed appearance of withdrawal symptoms (the decisive criterion for dependence). Symptoms manifested during withdrawal include restlessness, irritability, nervousness, anxiety, insomnia, and, occasionally or in susceptible patients, convulsions. These symptoms are hardly distinguishable from those considered indications for the use of benzodiazepines. Benzodiazepine withdrawal reactions are more likely to occur after abrupt cessation of prolonged or excessive dosage and are more pronounced in shorter-acting substances, but may also be evident after discontinuation of therapeutic dosages administered for no longer than 1–2 weeks.

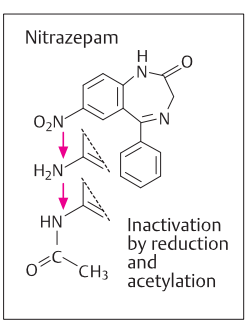
The table in ▶ Fig. 28.5**B** shows the elimination half-lives of individual benzodiazepines. In this group of drugs it is particularly difficult to match the correctly measured elimination half-life with the pharmacological duration of action, as they rarely coincide. This therapeutic experience is partly due to the fact that the dose–effect curves are not dependent simply on the concentration but, for instance, are "ineffective" in the lower range. Moreover, the reactivity of the target organ can alter in a short time. To give an example: a certain dose of a hypnotic is given at night, when it encounters a brain that is ready for sleep. When the same dose is given in the morning after a long refreshing sleep, the drug has no effect. The information regarding the $t_{1/2}$ or duration of action of the benzodiazepines can therefore only be a rough guide.

A. Biotransformation of benzodiazepines



B. Rate of elimination of benzodiazepines





Elimination half-lives of benzodiazepines

Drug	Indication	Mean $t^1/_2$
Midazolam	Induction of anesthesia	2 h
Triazolam	Short-acting hypnotic	3.5 h
Brotizolam	Short-acting hypnotic	6 h
Oxazepam	Intermediate-acting hypnotic	10 h
Lormetazapam	Intermediate-acting hypnotic	11 h
Temazapam	Intermediate-acting hypnotic	15 h
Flunitrazepam	Anxiolytic	25 h
Nitrazepam	Anxiolytic	28 h
Diazepam	Anxiolytic	60 h
Lorazepam	Antiepileptic	15 h
Clonazepam	Antiepileptic	24 h

Fig. 28.5

Pharmacotherapy of Depressive Illness

The term "depression" is used for a variety of states that are characterized by downswings in mood varying from slight to most severe. The principal types are:

- Endogenous depression, ranging from its severe form (major depression) to lighter cases (minor depression)
- Dysthymia (neurotic depression)
- Reactive depression as (overshooting) reaction to psychic insults or somatic illness

Endogenous depression generally follows a phasic course with intervals of normal mood. When mood swings do not change direction, unipolar depression is said to be present. Bipolar illness designates an alternation between depressive states and manic episodes. Besides devitalizing melancholia with its attendant burden of suffering, the behavior of patients in depression may vary from strongly inhibited to anxious, agitated, guilt-ridden, presuicidal, and so on. Depressive states are frequently associated with somatic symptoms; the patients project their mood disturbance into a physical ailment. Accordingly, many depressive patients initially visit a family physician or internist.

A separate group of drugs is available for the treatment of depression: antidepressants, also known as thymoleptics.

The pharmacotherapy of depression is a difficult undertaking. At the outset, it is necessary to determine the type of depression. For instance, in neurotic depression, psychotherapy may be sufficient. A reactive mood disorder calls for attempts to establish the causal link. In either condition, temporary use of antidepressants may be warranted. The proper indication for antidepressants is endogenous depression. However, even for this endogenous psychosis, it is difficult to evaluate the effectiveness of this drug class. One fundamental reason is the lack of experimental animal models of depression: the efficacy of drugs cannot be tested in experiments on animals. Moreover, depression is periodic in nature; spontaneous remission nearly always occurs. Intensive psychological support may also sometimes be effective in improving the condition of patients. According to some estimates, one-third of therapeutic success in moderately severe depression can be attributed to a placebo effect, one-third to intensive support, and the remaining one-third to use of antidepressant agents. In severe depression, pharmacotherapy may achieve somewhat more favorable results. Because objective documentation of therapeutic success is extraordinarily difficult, it is hardly surprising that no specific antidepressant has proved superior in comparison with others. About 30% of patients are resistant to currently available drug treatments. A workable general rule would be to prescribe tricyclic compounds (and venlafaxine) for severe depression, and selective serotonin reuptake inhibitors (SSRI) for moderately severe to mild cases. No scientifically convincing evidence is available for the "alternative" herbal medicine, St. John's wort *(Hypericum perforatum)*, although drug interactions are well documented.

It would be a major therapeutic error to administer a drive-enhancing drug such as amphetamine to a depressed patient with psychomotor inhibition (▶ Fig. 28.6A). Suicide would be an expected consequence.

The antidepressant effect of thymoleptics manifests after a prolonged latency; depending on the drug, days or even up to 3 weeks pass before subjective or objective improvement becomes noticeable (▶ Fig. 28.6A). In contrast, somatic effects are immediately evident; specifically, the interference with neuronal transmitter/modulator systems (norepinephrine, serotonin, acetylcholine, histamine, dopamine). Reuptake of released serotonin, norepinephrine, or both is impaired (→ elevated concentration in synaptic cleft) and/or receptors are blocked (example in A). These effects are demonstrable in animal studies and are the cause of acute adverse effects.

The importance of these phenomena for the antidepressant effect remains unclear. Presumably, adaptation of receptor systems to altered concentrations or actions of transmitter/modulator substances plays a role. The antidepressant mechanism of action remains to be elucidated.

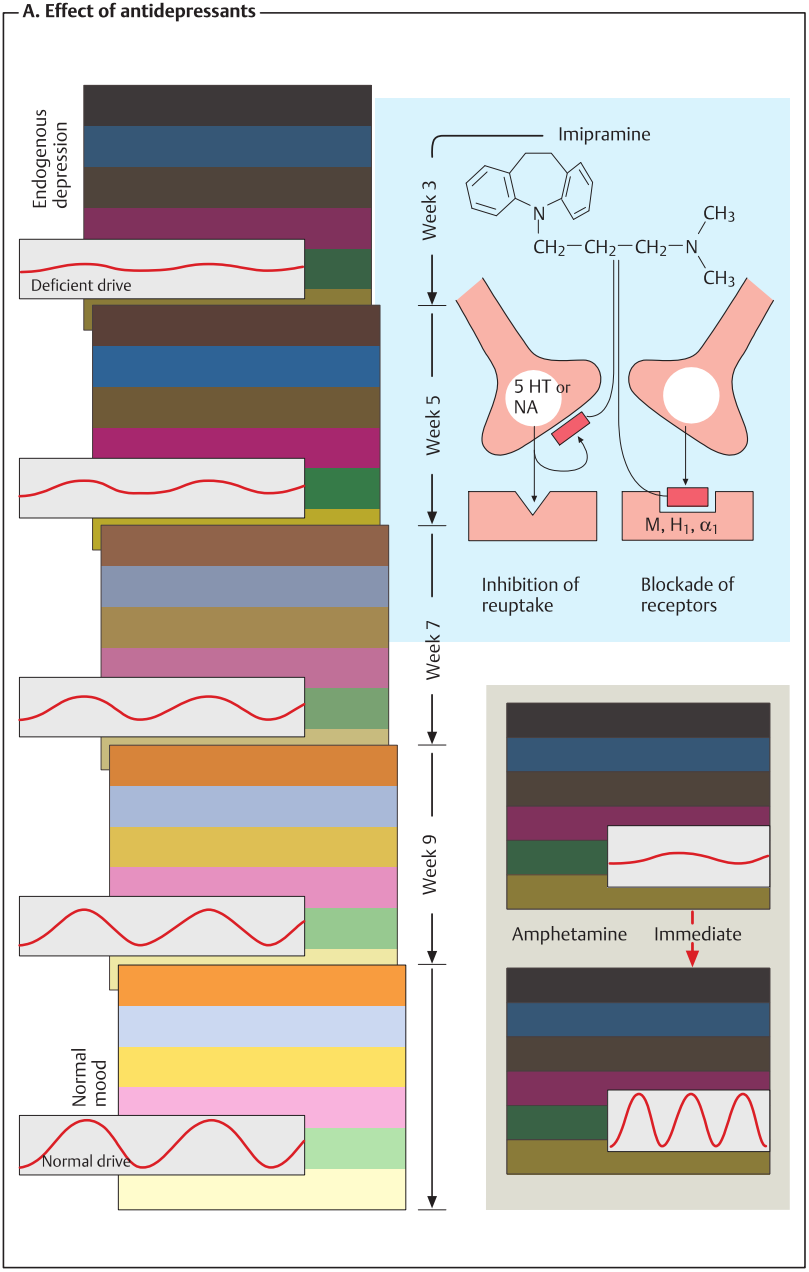

A. Effect of antidepressants
Endogenous depression
Deficient drive
Week 3
Week 5
Week 7
Week 9
Normal mood
Normal drive
Imipramine
N
CH3
CH2—CH2—CH2—N
CH3
5 HT or NA
M, H1, α1
Inhibition of reuptake
Blockade of receptors
Amphetamine
Immediate

Fig. 28.6

Antidepressants can be divided into three groups:

► **1. Tricyclic antidepressants (TCAs, ► Fig. 28.7A).** TCAs such as imipramine, desipramine, amitriptyline, and many analogue substances, possess a hydrophobic ring system. The central 7-membered ring increases the anneulation angle between the outer flanking rings. This moiety can also be tetracyclic (e.g., maprotiline). The ring system bears a side chain with a secondary or tertiary amine that can be protonated depending on its pK_a value. These substances can thus take on an amphiphilic character, permitting insertion into lipid membranes and enrichment in cellular structures. The basic structure of tricyclic antidepressants also explains their affinity for receptors and transmitter transport mechanisms. Receptor blockade is the chief cause of the adverse effects in this drug group, including: tachycardia, inhibition of glandular secretion (dry mouth), constipation, difficulty in micturition, blurred vision, and orthostatic hypotension (► Fig. 28.7A). A sedative action probably arising from antagonism at CNS H_1 histamine receptors, as obtained with amitriptyline, can be desirable. These side effects occur without any latency and are seen in animal studies and mentally healthy humans; on the other hand, "mood elevation" or a euphoriant effect does not occur in healthy humans.

► **2. Selective biogenic amine reuptake inhibitors.** These substances (e.g., fluoxetine) also possess a protonatable nitrogen atom and, instead of a larger ring system, contain simpler aromatic moieties. They also have amphiphilic character. Because their affinity for receptors is much less (no blockade of acetylcholine or norepinephrine receptors), acute adverse effects are less marked than those of tricyclic thymoleptics. Blockade of reuptake is confined to serotonin (5-HT). Antidepressant potency is equal to or slightly inferior to that of tricyclics. Fluoxetine has a long duration of action. Together with its active metabolite, it is eliminated with a half-life of several days. Besides fluoxetine, this group of inhibitors includes **citalopram, sertraline, paroxetine,** and a few other drugs. They are indicated in moderately severe depression and mood disorders. The frequency and severity of side effects are lower than with the tricyclic antidepressants.

Venlafaxine acts as a serotonin/norepinephrine reuptake inhibitor. Its efficacy is similar to that of the tricyclic antidepressants but it has weaker autonomic side effects. **Reboxetine** selectively inhibits reuptake of norepinephrine in some parts of the brain (SNRI). Whether it has a therapeutic benefit is doubtful.

Opipramol has a very weak action and is therefore indicated only for "generalized anxiety disorders, somatoform disorders." Despite —or perhaps because of—this vague indication, this drug is among the frequently prescribed psychotropic medications in Germany and other European countries.

► **3. Miscellaneous drugs.** The mechanism of action of **tianeptine,** recently approved in Germany though already on the market elsewhere for some time, is unclear. *Agomelatine,* a **melatonin receptor agonist**, is used to treat endogenous depression. As well as activating MT1 and MT2 receptors, it blocks the 5-HT_{2c} serotonin receptors.

In severe depression with psychomotor retardation, a moderate increase in drive may be beneficial. The monoamine oxidase inhibitor **moclobemide,** which leads to an increase in the CNS concentrations of biogenic amines, is used for this indication. The risk of provoking suicide must be borne in mind.

A. Antidepressants: activity profiles

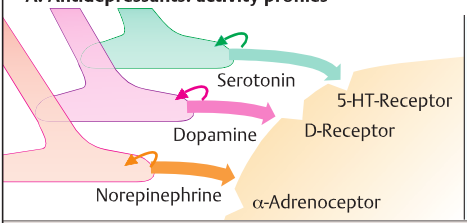
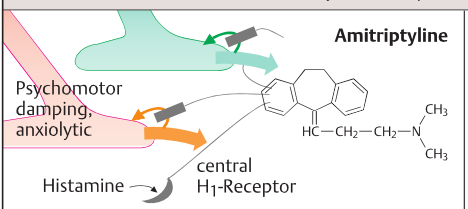
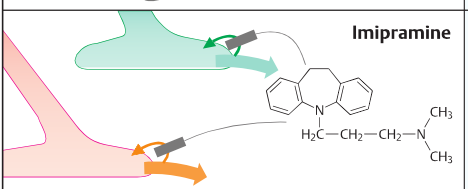
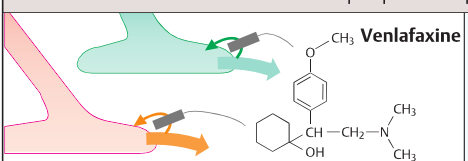
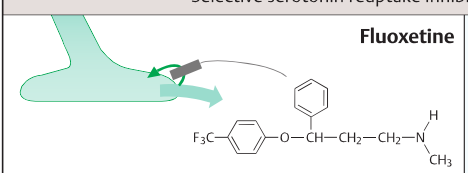
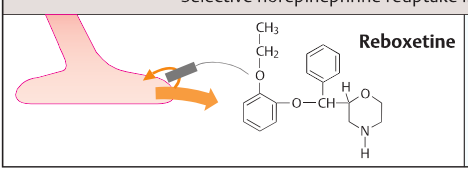
	Indication	Adverse effects
		
Tricyclic antidepressants		
	Anxious, agitated Severe endogenous depression	Parasympatholytic effects: e.g., tachycardia, dry mouth, constipation, difficult urination **Caution:** closed-angle glaucoma
	Drive normal Severe endogenous depression	α1-Blockade: orthostatic hypotension
Selective serotonin and norepinephrine reuptake inhibitors (SSNRI)		
	Psychomotor inhibition Depression when tricyclic antidepressants are ineffective or not tolerated	In high dose: cardiodepression Fewer autonomic side effects
Selective serotonin reuptake inhibitors (SSRI)		
	Psychomotor inhibition Mild depression, depressed mood, anxiety symptoms	Nervousness, sleep disorder, poor appetite, weight loss
Selective norepinephrine reuptake inhibitors (SNRI)		
	Severe depression when increased drive is desired	Autonomic disorders (insomnia, micturition disturbances, cardiac disorders)

Fig. 28.7

Pharmacotherapy of Manic States

The manic phase is characterized by exaggerated elation, flight of ideas, and a pathologically increased psychomotor drive. This is symbolically illustrated in ▶ Fig. 28.8A by a disjointed structure and aggressive color tones. The patients are overconfident, continuously active, show progressive incoherence of thought and loosening of associations, and act irresponsibly (financially, sexually, etc.).

Agents to Treat Manic States

Lithium. Lithium is the lightest of the alkali metal atoms (▶ Fig. 28.8A), of which family sodium and potassium have special significance for the organism. Lithium ions (Li^+) distribute nearly evenly in the extracellular and intracellular fluid compartments and thus build up only a small concentration gradient across the cell membrane. The lithium ion cannot be transported by the membrane Na^+/K^+-ATPase. Intracellularly, lithium ions interfere with signal transduction mechanisms. For instance, they reduce the hydrolysis of inositol triphosphate, leading to a reduced sensitivity to transmitters of nerve cells. In addition, the metabolism of transmitters is thought to be altered in the presence of lithium ions. These and other biochemical findings observed after administration of lithium do not provide a satisfactory explanation for the therapeutic effect of this "simple" pharmaceutical, particularly so because the somatic disturbance underlying mania remains unknown. As in endogenous depression, it is surmised that imbalances between different transmitter systems are at fault. Remarkably, Li^+ ions do not exert psychotropic effects in healthy humans, although they elicit the typical adverse effects.

▶ **Indications for lithium therapy.**

1. Acute treatment of manic phase; therapeutic response develops only in the course of several days (▶ Fig. 28.8A).
2. Long-term administration (6–12 months until full effect reached) for the prophylaxis of both manic and depressive phases of bipolar illness (▶ Fig. 28.8A).
3. Adjunctive therapy in severe therapy-resistant depressions.

Lithium therapy of acute mania is difficult because of the **narrow margin of safety** and because the patient being treated lacks insight. Therapeutic plasma levels should be closely monitored and kept between 0.8 and 1.2 mM in fasting morning blood samples. For prevention of relapse, slightly lower blood levels of 0.5–0.8 mM are recommended. Adverse effects that occur at therapeutic serum concentration during long-term intake of lithium salts include renal (diabetes insipidus) and endocrine manifestations (goiter and/or hypothyroidism, glucose intolerance, hyperparathyroidism, sexual dysfunction). At concentrations >1.2–1.5 mM, signs of mild toxicity are evident, including a fine hand tremor, weakness, fatigue, and abdominal complaints. As blood levels rise further, decreased ability to concentrate, agitation, confusion, and cerebellar signs are noted. In the most severe cases of poisoning, seizures may occur and the patient may lapse into a comatose state. During lithium therapy, fluctuations in blood level are quite common because changes in dietary daily intake of NaCl or fluid losses (diarrhea, diuretics) can markedly alter renal elimination of lithium. Lithium therapy thus requires special diligence on the part of the physician and cooperation on the part of the patient or his or her relatives.

Bipolar disorder consists of alternating depressive phases and manic periods. This disorder can be alleviated or suppressed by use of mood-stabilizing serotonin or dopamine reuptake inhibitors (e.g., olanzapine) or antiepileptic drugs such as valproic acid, carbamazepine, and lamotrigine. If a depressive phase occurs despite this long-term therapy, antidepressants that do not increase drive must be given to avoid the risk of intensifying a subsequent manic period. Lithium therapy is indicated if a manic phase occurs.

Asenapine, a neuroleptic, can be given sublingually to treat mania.

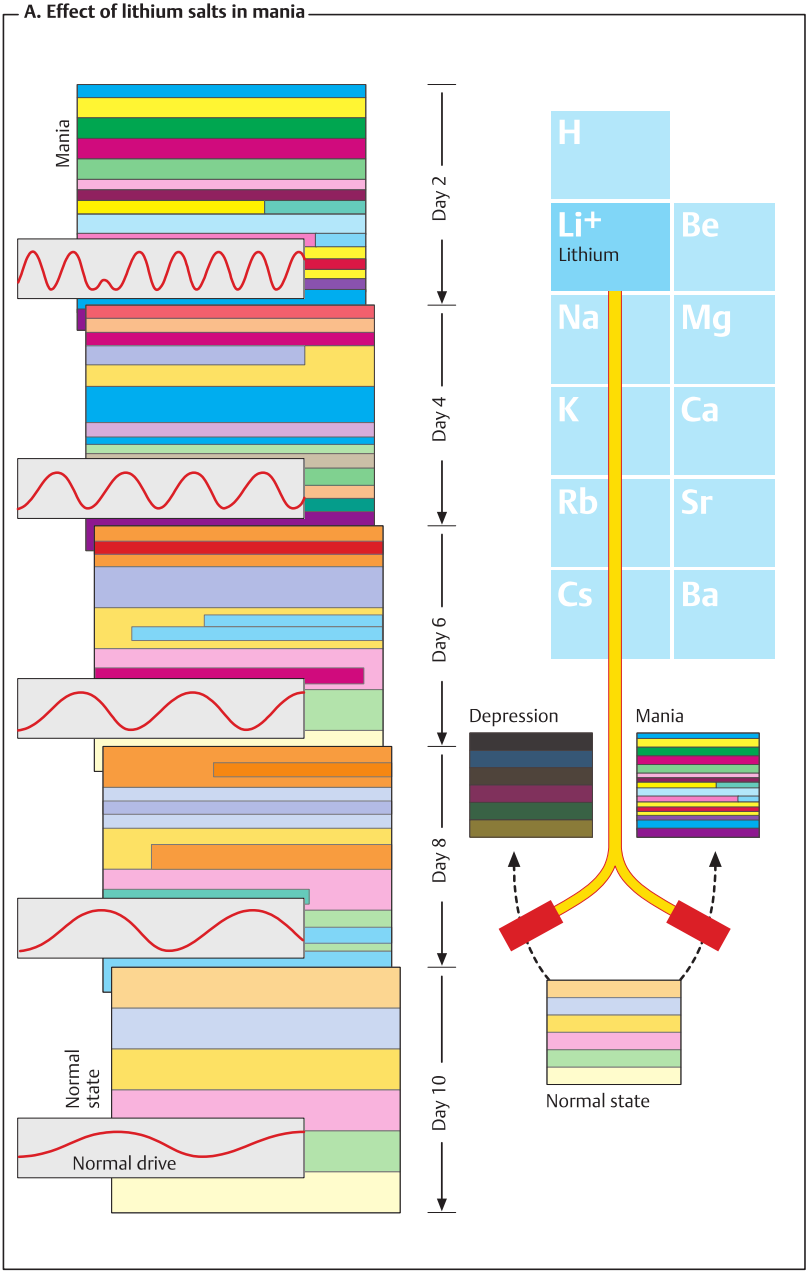

A. Effect of lithium salts in mania
Mania
Day 2
Day 4
Day 6
Day 8
Day 10
Normal state
Normal drive
H
Li+
Lithium
Be
Na
Mg
K
Ca
Rb
Sr
Cs
Ba
Depression
Mania
Normal state

Fig. 28.8

Pharmacotherapy of Schizophrenia

Schizophrenia is an endogenous psychosis of episodic character; in most cases, recovery is incomplete (residual defects, burned-out end stage). The different forms of schizophrenic illness will not be considered here. From a therapeutic perspective, it is relevant to differentiate between since both symptom complexes respond differently to antipsychotic drugs.

- Positive signs including delusions, hallucinations, disorganized speech, behavior disturbance; and
- Negative signs, such as social isolation, affective flattening, avolition, poverty of speech, and anhedonia

since both symptom complexes respond differently to antipsychotic drugs.

► **Neuroleptics.** After neuroleptic treatment of a psychotic episode is initiated, the antipsychotic effect proper manifests following a latent period. Acutely, psychomotor damping with anxiolysis and distancing is noted. Tormenting paranoid ideas and hallucinations lose their subjective importance (► Fig. 28.9**A**, dimming of flashy colors); initially, however, the psychotic process persists but then wanes gradually over the course of several weeks.

Complete normalization often cannot be achieved. Even though a "cure" is unrealizable, these changes signify success because (a) the patient obtains relief from the torment of psychotic personality changes; (b) care of the patient is facilitated; and (c) return into a familiar community environment is accelerated. Neuroleptic therapy utilizes different drug classes, namely phenothiazines, butyrophenones, and the atypical neuroleptics.

The **phenothiazines** were developed from the H_1 antihistamine promethazine: prototype chlorpromazine (no longer on the market) and its congeners, such as fluphenazine, levopromazine, perazine, perphenazine, prothipendyl, and thioridazine, have a planar tricyclic ring system and a side chain containing a protonatable nitrogen atom. Phenothiazines exhibit affinity for various receptors and exert corresponding antagonistic actions. Blockade of dopamine receptors, specifically in the mesolimbic prefrontal system, appears important for the antipsychotic effect. The latency of the antipsychotic effect suggests that adaptive processes induced by receptor blockade play a role in the therapeutic response. Besides affinity for D_2 dopamine receptors, neuroleptics also exhibit varying affinity to other receptors, including M-ACh receptors, α_1-adrenoceptors, and histamine H_1 and 5-HT receptors. Antagonism at these receptors contributes to the adverse effects. Affinity profiles of "classical" neuroleptics (phenothiazine and butyrophenone derivatives) differ significantly from those of newer atypical drugs (p. 234), in which affinity for 5-HT receptors predominates.

Neuroleptics *do not have anticonvulsant* activity.

Chronic use of neuroleptics can on occasion give rise to *hepatic damage* associated with cholestasis. A very rare, but dramatic, adverse effect is the *malignant neuroleptic syndrome* (skeletal muscle rigidity, hyperthermia, stupor), which can have a fatal outcome in the absence of intensive countermeasures (including treatment with dantrolene).

With other phenothiazines (e.g., fluphenazine with a piperazine side chain substituent), antagonism at other receptor types tends to recede into the background vis-à-vis the blockade of D_2 dopamine receptors. In ► Fig. 28.10**B** the D_2 receptor affinity of the drugs concerned is defined as ++, while the differences in absolute affinity for the other receptors are ignored.

The **butyrophenones** (prototype haloperidol) were introduced after the phenothiazines. With these agents, blockade of D_2 receptors predominates entirely (► Fig. 28.10**B**). Antimuscarinic and antiadrenergic effects are attenuated. The "extrapyramidal" motor disturbances that result from D_2 receptor blockade are, however, preserved and constitute the clinically most important adverse reactions that often limit therapy.

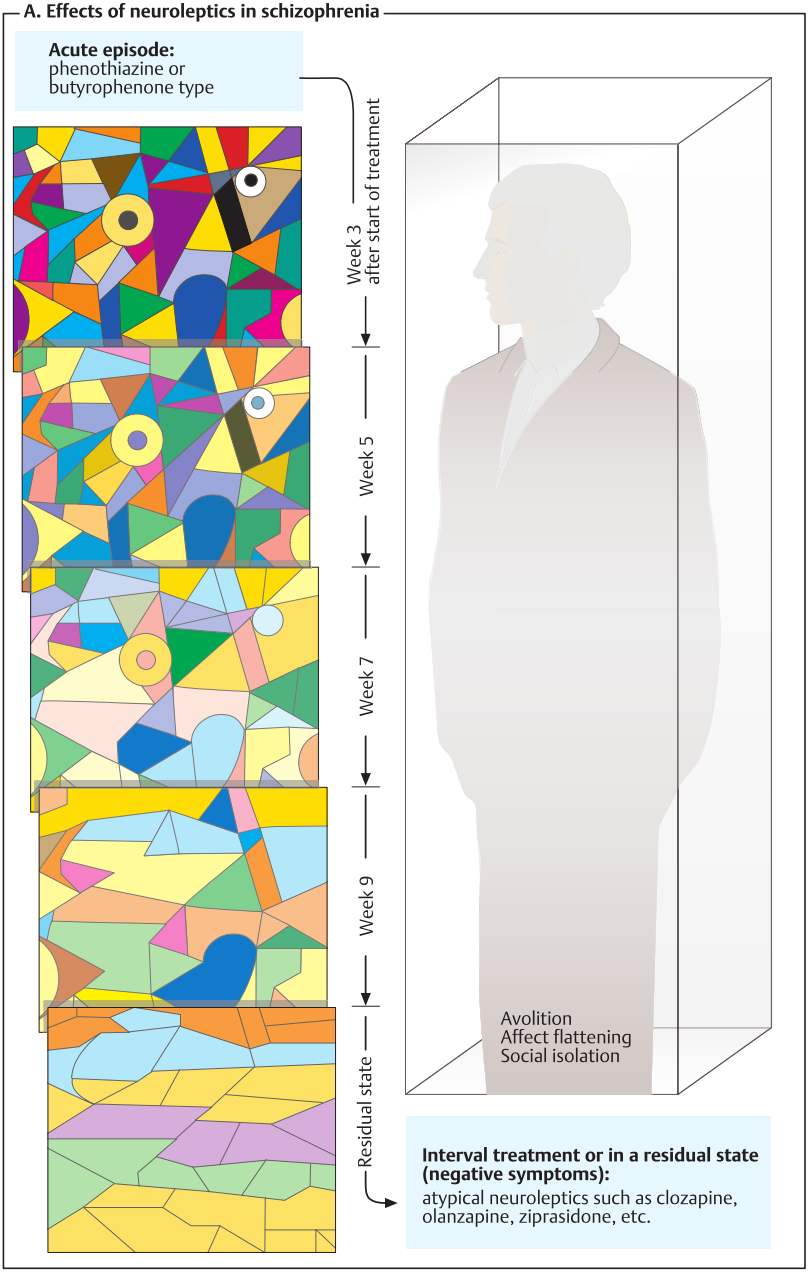

A. Effects of neuroleptics in schizophrenia
Acute episode:
phenothiazine or
butyrophenone type
Week 3
after start of treatment
Week 5
Week 7
Week 9
Residual state
Avolition
Affect flattening
Social isolation
Interval treatment or in a residual state
(negative symptoms):
atypical neuroleptics such as clozapine,
olanzapine, ziprasidone, etc.

Fig. 28.9

Early dyskinesias occur immediately after neuroleptization and are manifested by involuntary abnormal movements in the head, neck, and shoulder region. After treatment of several weeks to months, a *parkinsonian syndrome* (pseudoparkinsonism) (p. 334) or *akathisia* (motor restlessness) may develop. All these disturbances can be treated by administration of antiparkinsonian drugs of the anticholinergic type, such as biperiden. As a rule, these disturbances disappear after withdrawal of neuroleptic medication. *Tardive dyskinesia* may become evident after chronic neuroleptization for several years, particularly when the drug is discontinued. Its postulated cause is a hypersensitivity of the dopamine receptor system. The condition is exacerbated by administration of anticholinergics.

The butyrophenones carry an increased risk of adverse motor reactions because they lack anticholinergic activity and, hence, are prone to upset the balance between striatal cholinergic and dopaminergic activity.

Atypical neuroleptics differ in structure and pharmacological properties from the aforementioned drug groups. Extrapyramidal motor reactions are absent or less prevalent. The antipsychotic effect involves not only the positive but also the negative symptoms. In the case of *clozapine,* it was assumed at first that the drug acted as a selective antagonist at D_4 dopamine receptors. Subsequently, however, the drug was recognized as a high-affinity ligand and antagonist at other receptors (▶ Fig. 28.10**B**). Clozapine can be used when other neuroleptics have to be discontinued because of extrapyramidal motor reactions. Clozapine may cause agranulocytosis, necessitating close hematological monitoring. It produces marked *sedation.*

Olanzapine is structurally related to clozapine; thus far the risk of agranulocytosis appears to be low or absent.

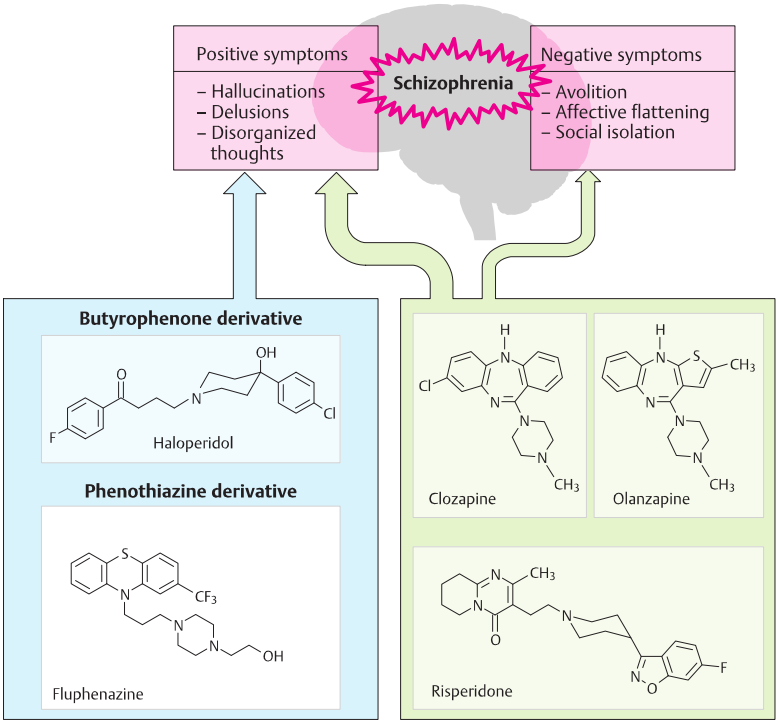
Loxapine is available as a powder for inhalation in the acute management of agitated patients.

Risperidone differs in structure from the aforementioned drugs; it possesses relatively lower affinity for all "non–D_2 receptors." *Paliperidone* is a metabolite of risperidone.

Ziprasidone shows high affinity for 5-HT_{2A} receptors. Remarkably, this new substance also stimulates 5-HT_{1A} receptors, which translates into an antidepressant effect. Ziprasidone particularly influences negative symptoms, its effect on positive symptoms reportedly being equivalent to that of classical neuroleptics. Adverse effects due to blockade of M-ACh, H_1 and α_1-receptors are comparatively weak. Central disturbances (giddiness, ataxia, etc.) may occur. Moreover, QT interval prolongation has been observed; concurrent administration of QT-prolonging drugs must therefore be avoided. The neuroleptic *aripiprazole* can be regarded as similar to ziprasidone.

▶ **Uses.** Management of acute psychotic phases requires high-potency neuroleptics. In highly agitated patients, i.v. injection of haloperidol may be necessary. The earlier therapy is started, the better is the clinical outcome. Most schizophrenic patients require maintenance therapy for which a low dosage can be selected. For stabilization and prevention of relapse, atypical neuroleptics are especially suited since they improve negative symptoms in responsive patients. The patients need good care and, if possible, integration into a suitable milieu. Difficulties arise because patients do not take their prescribed medication (N.B.: counseling of both patient and caregivers). To circumvent lack of compliance, depot preparations have been developed, e.g., fluphenazine decanoate (i.m. every 2 weeks) and haloperidol decanoate (i.m. every 4 weeks), which yield stable blood levels for the period indicated.

A. Conventional and atypical neuroleptics



B. Receptor affinity profile with reference to D_2 dopamine receptor

	D_2	M-ACh	α_1	H_1	5-HT_{2A}	5-HT_{1A}
Fluphenazine	++	–	+	+	+	–
Haloperidol	++	+	+	+	+	–
Clozapine	++	+++	+++	+++	+++	–
Olanzapine	++	++	++	+++	+++	–
Risperidone	++	–	++	++	++	–
Ziprasidone	++	+	+	+	+++	!++!

The receptor affinities of each drug are compared in relation to its D_2 receptor affinity, arbitrarily set at (++); antagonistic effects, except for ziprasidone (5-HT_{1A} agonism)

Fig. 28.10

Hypothalamic and Hypophyseal Hormones

The endocrine system is controlled by the brain. **Nerve cells of the hypothalamus** synthesize and release messenger substances that regulate adenohypophyseal (AH) hormone release or that are themselves secreted into the body as hormones. The latter comprise the so-called **neurohypophyseal (NH) hormones.**

The axonal processes of hypothalamic neurons project to the neurohypophysis, where they store the *nonapeptides vasopressin* (= antidiuretic hormone, ADH; p. 180) and *oxytocin* (p. 144) and release them on demand into the blood. Therapeutically, these peptide hormones are given parenterally or via the nasal mucosa.

The **hypothalamic releasing hormones** are *peptides.* They reach their target cells in the AH lobe by way of a portal vascular route consisting of two serially connected capillary beds. The first of these lies in the hypophyseal stalk, the second corresponds to the capillary bed of the AH lobe. Here, the hypothalamic hormones diffuse from the blood to their target cells, whose activity they control. Hormones released from the AH cells enter the blood, in which they are distributed to peripheral organs.

▶ **Nomenclature of releasing hormones.** (RH: releasing hormone. RIH: release-inhibiting hormone.)

GnRH, gonadotropin-RH = gonadorelin: stimulates the release of FSH (follicle-stimulating hormone) and LH (luteinizing hormone).

TRH, thyrotropin-RH (protirelin): stimulates the release of **TSH** (thyroid-stimulating hormone = thyrotropin).

CRH, corticotropin-RH: stimulates the release of ACTH (adrenocorticotropic hormone = corticotropin).

GHRH, growth hormone-RH = somatorelin: stimulates the release of GH (growth hormone = STH, somatotropic hormone).

GHRIH = somatostatin: inhibits release of STH (and also other peptide hormones including insulin, glucagon, and gastrin).

PRIH inhibits the release of prolactin and is identical with dopamine.

▶ **Therapeutic control of AH cells. GnRH** is used in *hypothalamic infertility in women* to stimulate FSH and LH secretion and to induce ovulation. For this purpose, it is necessary to mimic the physiological intermittent release ("pulsatile," approximately every 90 minutes) by means of a programmed infusion pump.

Gonadorelin superagonists are GnRH analogues that bind with very high avidity to GnRH receptors of AH cells. As a result of the nonphysiological uninterrupted receptor stimulation, initial augmentation of FSH and LH output is followed by a prolonged decrease. *Buserelin, leuprorelin, goserelin,* and *triptorelin* (the "relins") are used to shut down gonadal function in this manner ("chemical castration," e.g., in advanced prostatic carcinoma). **Gonadorelin receptor antagonists,** such as cetrorelix and ganirelix, block the GnRH receptors of AH cells and thus cause cessation of gonadotropin release.

The **dopamine D_2 agonists** (p. 128), such as bromocriptine, inhibit prolactin-releasing AH cells (indications: suppression of lactation, prolactin-producing tumors).

Octreotide and **lanreotide** are somatostatin analogues that are metabolized more slowly than the parent peptide. They are used in the treatment of somatostatin-secreting pituitary tumors (acromegaly). **Pasireotide** halts the release of ACTH from AH tumors in Cushing disease.

Acromegaly can also be treated with a somatotropin receptor antagonist. Growth hormone requires mediation by somatomedins for many of its actions. These are chiefly formed in the liver, including the important somatomedin C (= insulin-like growth factor 1, IGF-1). *Pegvisomant* is an antagonist at the GH receptor and inhibits the production of IGF-1. Conversely, IGF-1 can also be replaced by mecasermin, a recombinant form, if production is deficient.

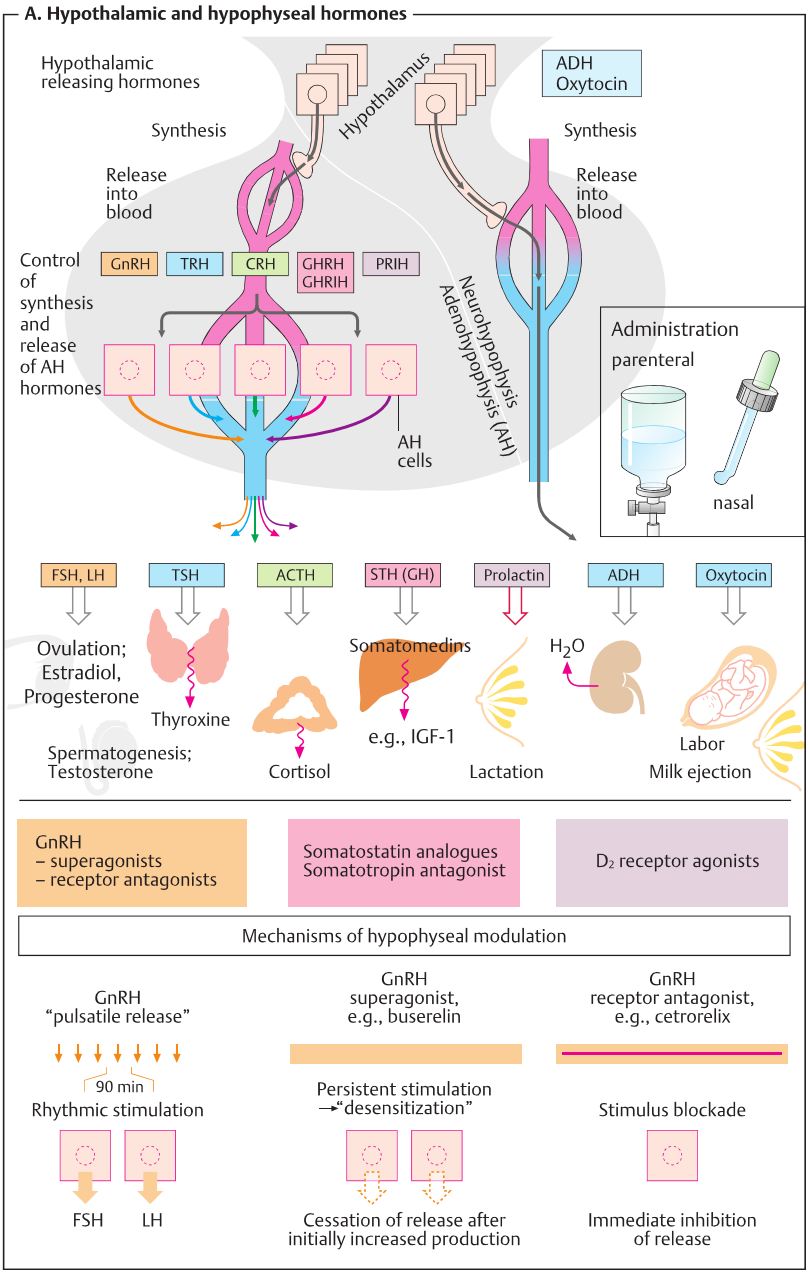

A. Hypothalamic and hypophyseal hormones
Hypothalamic releasing hormones
Synthesis
Release into blood
Hypothalamus
ADH Oxytocin
Synthesis
Release into blood
Control of synthesis and release of AH hormones
GnRH
TRH
CRH
GHRH GHRIH
PRIH
AH cells
Neurohypophysis
Adenohypophysis (AH)
Administration
parenteral
nasal
FSH, LH
TSH
ACTH
STH (GH)
Prolactin
ADH
Oxytocin
Ovulation; Estradiol, Progesterone
Spermatogenesis; Testosterone
Thyroxine
Cortisol
Somatomedins
e.g., IGF-1
Lactation
H_2O
Labor
Milk ejection
GnRH – superagonists – receptor antagonists
Somatostatin analogues Somatotropin antagonist
D_2 receptor agonists
Mechanisms of hypophyseal modulation
GnRH "pulsatile release"
90 min
Rhythmic stimulation
FSH
LH
GnRH superagonist, e.g., buserelin
Persistent stimulation →"desensitization"
Cessation of release after initially increased production
GnRH receptor antagonist, e.g., cetrorelix
Stimulus blockade
Immediate inhibition of release

Fig. 29.1

Thyroid Hormone Therapy

Thyroid hormones accelerate metabolism. Their release (▶ Fig. 29.2**A**) is regulated by the hypophyseal glycoprotein TSH, whose release, in turn, is controlled by the hypothalamic tripeptide TRH. Secretion of TSH declines as the blood level of thyroid hormones rises; by means of this negative feedback mechanism, hormone production is "automatically" adjusted to demand.

The thyroid releases predominantly thyroxine (T_4). However, the active form appears to be triiodothyronine (T_3); T_4 is converted in part to T_3, receptor affinity in target organs being 10-fold higher for T_3. The effect of T_3 develops more rapidly and has a shorter duration than does that of T_4. Plasma elimination $t_{1/2}$ for T_4 is about 7 days; that for T_3, however, is only 1.5 days. Conversion of T_4 to T_3 releases iodide; 150 µg T_4 contains 100 µg of iodine.

For therapeutic purposes, T_4 is chosen, although T_3 is the active form and better absorbed from the gut. With T_4 administration, more constant blood levels can be achieved because T_4 degradation is so slow. Since T_4 absorption is maximal from an empty stomach, T_4 is taken about half an hour before breakfast.

▶ **Replacement therapy of hypothyroidism.** Whether primary, i.e., caused by thyroid disease, or secondary, i.e., resulting from TSH deficiency, hypothyroidism is treated by oral administration of T_4. Since too rapid activation of metabolism entails the hazard of cardiac overload (angina pectoris, myocardial infarction), therapy is usually started with low doses and gradually increased. The final maintenance dose required to restore a euthyroid state depends on individual needs (~150 µg/day).

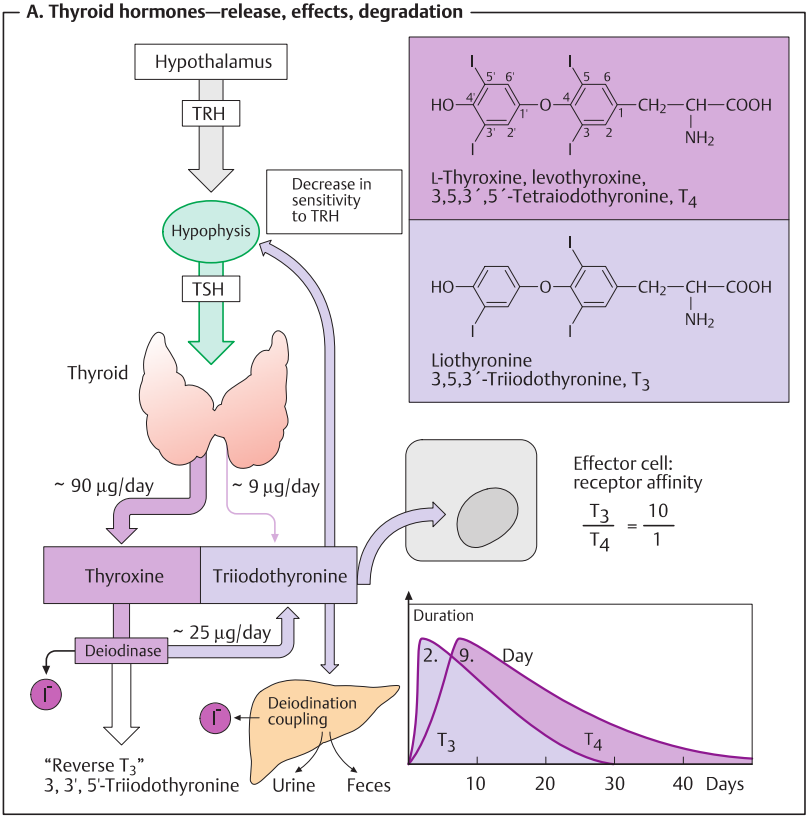
▶ **Thyroid suppression therapy of euthyroid goiter** (▶ **Fig. 29.2B**). The cause of goiter (struma) is usually a dietary deficiency of iodine. Owing to increased TSH action, the thyroid is activated to raise utilization of the little iodine available to a level at which hypothyroidism is averted. Accordingly, the thyroid increases in size. In addition, intrathyroid depletion of iodine stimulates growth.

Because of the negative feedback regulation of thyroid function, thyroid activation can be inhibited by administration of T_4 doses equivalent to the endogenous daily output (~150 µg/day). Deprived of stimulation, the inactive thyroid regresses in size.

If a euthyroid goiter has not persisted for too long, increasing iodine supply (with potassium iodide tablets) can also be effective in reversing overgrowth of the gland.

In older patients with goiter due to iodine deficiency, there is a risk of provoking hyperthyroidism by increasing iodine intake (▶ Fig. 29.3**B**). During chronic maximal stimulation, thyroid follicles can become independent of TSH stimulation ("autonomous tissue" containing TSH receptor mutants with spontaneous "constitutive activity"). If the iodine supply is increased, thyroid hormone production increases while TSH secretion decreases owing to feedback inhibition. The activity of autonomous tissue, however, persists at a high level; thyroxine is released in excess, resulting in iodine-induced hyperthyroidism.

▶ **Iodized salt prophylaxis.** Goiter is endemic in regions where soils are deficient in iodine. Use of iodized table salt allows iodine requirements (150–300 µg/day) to be met and effectively prevents goiter.


A. Thyroid hormones—release, effects, degradation
Hypothalamus
TRH
Decrease in sensitivity to TRH
Hypophysis
TSH
Thyroid
~ 90 µg/day
~ 9 µg/day
Thyroxine
Triiodothyronine
~ 25 µg/day
Deiodinase
I⁻
Deiodination coupling
"Reverse T3"
3, 3', 5'-Triiodothyronine
Urine
Feces
L-Thyroxine, levothyroxine,
3,5,3´,5´-Tetraiodothyronine, T4
Liothyronine
3,5,3´-Triiodothyronine, T3
Effector cell:
receptor affinity
T3/T4 = 10/1
Duration
2.
9.
Day
T3
T4
10
20
30
40
Days

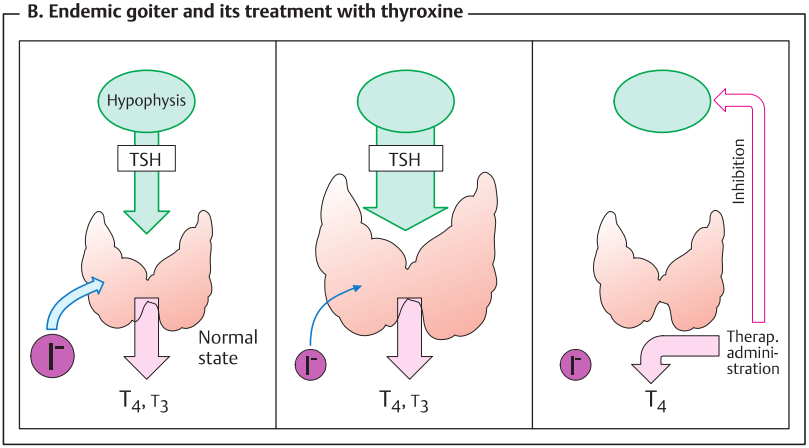

B. Endemic goiter and its treatment with thyroxine
Hypophysis
TSH
I⁻
Normal state
T4, T3
TSH
I⁻
T4, T3
Inhibition
I⁻
Therap. administration
T4

Fig. 29.2

Hyperthyroidism and Antithyroid Drugs

► **Hyperthyroidism.** Thyroid overactivity in Graves disease (► Fig. 29.3**A**) results from formation of IgG antibodies that bind to and activate TSH receptors. Consequently, there is overproduction of hormone with cessation of TSH secretion. Graves disease can abate spontaneously after 1–2 years; therefore, initial therapy consists in reversible suppression of thyroid activity by means of antithyroid drugs. In other forms of hyperthyroidism, such as hormone-producing (morphologically benign) thyroid adenoma, the preferred therapeutic method is removal of tissue, either by surgery or by administration of iodine-131 (^{131}I) in sufficient dosage. Radioiodine is enriched in thyroid cells and destroys tissue within a sphere of a few millimeters by emitting β-particles (electrons) during its radioactive decay.

Antithyroid drugs inhibit thyroid function. Release of thyroid hormone (► Fig. 29.3**C**) is preceded by a chain of events. A membrane Na^+/I^- symporter actively accumulates iodide in thyroid cells (the required energy comes from an Na^+/K^+-ATPase located in the basolateral membrane region); this is followed by oxidation to iodine, iodination of tyrosine residues in thyroglobulin, conjugation of two diiodotyrosine groups, and formation of T_4 moieties. These reactions are catalyzed by thyroid peroxidase, which is localized in the apical border of the follicular cell membrane. T_4-containing thyroglobulin is stored inside the thyroid follicles in the form of thyrocolloid. Upon endocytotic uptake, colloid undergoes lysosomal enzymatic hydrolysis, enabling thyroid hormone to be released as required. A "thyrostatic" effect can result from inhibition of synthesis or release. When synthesis is arrested, the antithyroid effect develops after a delay, as stored colloid continues to be utilized.

► **Antithyroid drugs for long-term therapy** (► **Fig. 29.3C**). **Thiourea derivatives** (thioamides) inhibit peroxidase and, hence, hormone synthesis. To restore a euthyroid state, two therapeutic principles can be applied in Graves disease: (a) monotherapy with a thioamide, with gradual dose reduction as the disease abates; (b) administration of high doses of a thioamide, with concurrent administration of thyroxine to offset diminished hormone synthesis. Adverse effects of thioamides are rare, but the possibility of agranulocytosis has to be kept in mind.

Perchlorate, given orally as the sodium salt, inhibits the iodide pump. Adverse reactions include aplastic anemia. Compared with thioamides, its therapeutic importance is low.

► **Short-term thyroid suppression** (► **Fig. 29.3C**). **Iodine in high dosage** (> 6000 µg/day) exerts a transient "thyrostatic" effect in hyperthyroid, but usually not in euthyroid, individuals. Since release is also blocked, the effect develops more rapidly than does that of thioamides.

Clinical applications include preoperative suppression of thyroid secretion according to *Plummer* with *Lugol* solution (5% iodine + 10% potassium iodide, 50–100 mg iodine/day for a maximum of 10 days). In thyrotoxic crisis, Lugol solution is given together with thioamides. β-Blockers are given to counteract thyroid hormone-induced cardiac stimulation and a glucocorticoid to inhibit thyroid inflammation and induce immunosuppression. *Adverse effects:* allergies. *Contraindications:* iodine-induced thyrotoxicosis.

Lithium ions inhibit thyroxine release. Lithium salts can be used instead of iodine for rapid thyroid suppression in iodine-induced thyrotoxicosis. Regarding administration of lithium in manic-depressive illness, see p. 230.

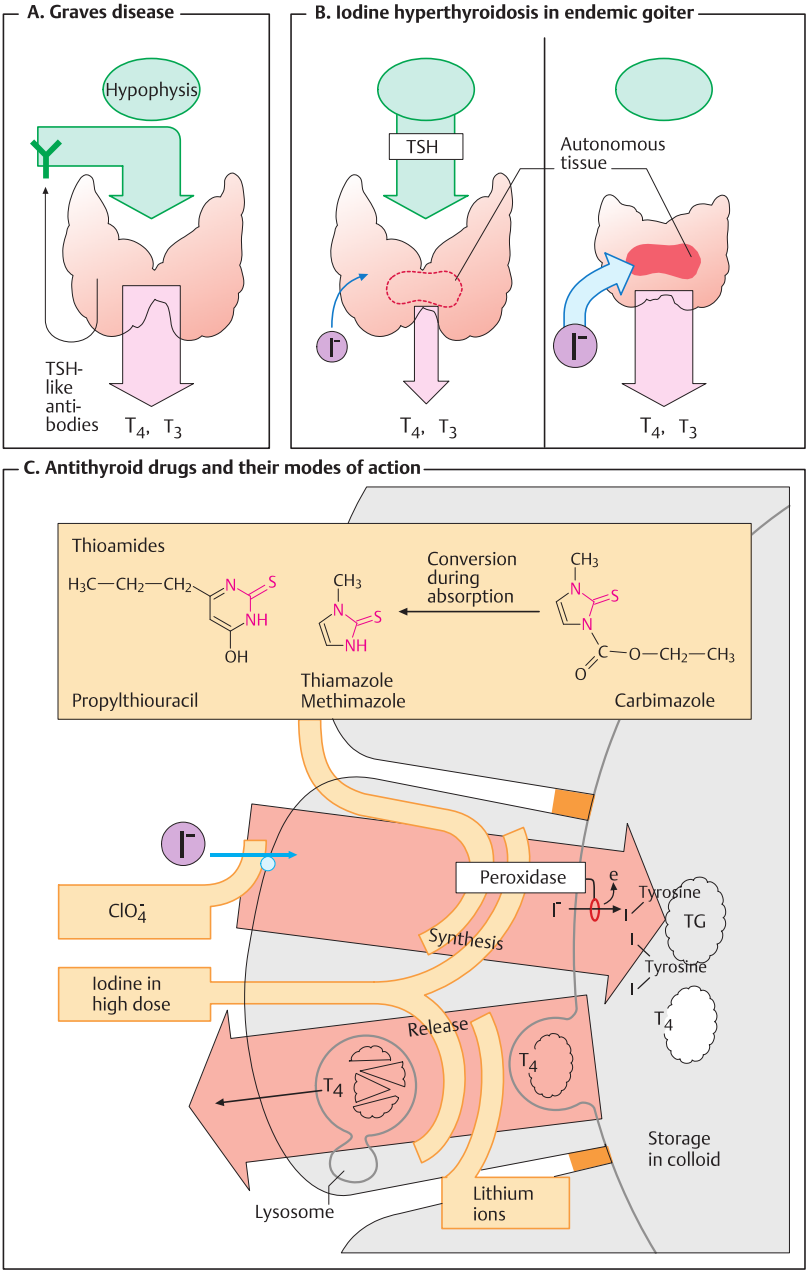

A. Graves disease
Hypophysis
TSH-like anti-bodies
T_4, T_3
B. Iodine hyperthyroidosis in endemic goiter
TSH
Autonomous tissue
I^-
T_4, T_3
T_4, T_3
C. Antithyroid drugs and their modes of action
Thioamides
Conversion during absorption
Propylthiouracil
Thiamazole
Methimazole
Carbimazole
I^-
ClO_4^-
Iodine in high dose
Peroxidase
e
Tyrosine
TG
Synthesis
Release
T_4
Storage in colloid
Lysosome
Lithium ions

Fig. 29.3

Glucocorticoid Therapy

The adrenal cortex (AC) produces the *glucocorticoid cortisol* (hydrocortisone) in the zona fasciculata and the *mineralocorticoid aldosterone* in the zona glomerulosa. Both steroid hormones are vital in adaptation responses to stress situations, such as disease, trauma, or surgery. Cortisol secretion is stimulated by hypophyseal ACTH (adrenocorticotropic hormone); aldosterone secretion by angiotensin II in particular (p. 142). In the liver, cortisol stimulates gluconeogenesis from amino acids and protects the body against hypoglycemia if no nourishment has been ingested for a long period and hepatic glycogen stores are exhausted. It also appears to prevent excessive inflammatory reactions. Aldosterone stimulates renal reabsorption of Na^+, Cl^-, and H_2O, thus counteracting a reduction in extracellular fluid volume.

► **I. Replacement therapy.** In AC failure *(primary adrenocortical insufficiency;* Addison disease), both *cortisol* and *aldosterone* must be replaced; when ACTH production is deficient *(secondary adrenocortical insufficiency), cortisol alone* needs to be replaced. Cortisol is effective when given orally (30 mg/day, ⅔ a.m., ⅓ p.m.). In stress situations, the dose is raised 5- to 10-fold. Aldosterone is poorly effective via the oral route; instead, the mineralocorticoid fludrocortisone (0.1 mg/day) is given.

► **II. Pharmacodynamic therapy with glucocorticoids (► Fig. 29.4A).** In unphysiologically high concentrations, cortisol or other glucocorticoids suppress all phases (exudation, proliferation, scar formation) of the inflammatory reaction. This effect is mediated by multiple components involving alterations in gene transcription. Firstly, the glucocorticoid receptor complex acts as a transcription factor to promote the expression of certain anti-inflammatory genes, e.g., lipocortin, which inhibits phospholipase A_2. Secondly, the complex can trap other transcription factors that are actually responsible for the production of proinflammatory proteins. This affects synthesis of several proteins that participate in the inflammatory process, including interleukins (p. 304) and other cytokines, phospholipase A_2 (p. 198), and cyclooxygenase-2 (p. 200). At very high dosage, nongenomic effects via membrane-bound receptors may also contribute.

► **Desired effects.** As *antiallergics, immunosuppressants,* or *anti-inflammatory* drugs, glucocorticoids display excellent efficacy against "undesired" inflammatory reactions, such as allergy, autoimmune diseases, etc.

► **Unwanted effects.** With *short-term systemic use,* glucocorticoids are practically free of adverse effects, even at the highest dosage. **Long-term use** is likely to cause changes mimicking the signs of **Cushing syndrome** (endogenous overproduction of cortisol). Sequelae of the anti-inflammatory action are lowered resistance to infection and delayed wound healing. Sequelae of exaggerated glucocorticoid action are (a) increased gluconeogenesis and release of glucose, insulin-dependent conversion of glucose to triglycerides (adiposity mainly noticeable in the face, neck, and trunk), and "steroid-diabetes" if insulin release is insufficient; (b) increased protein catabolism with atrophy of skeletal musculature (thin extremities), osteoporosis, growth retardation in infants, and skin atrophy. Sequelae of the intrinsically weak, but now manifest, mineralocorticoid action of cortisol are salt and fluid retention, hypertension, edema; and KCl loss with danger of hypokalemia. Psychic changes, chiefly in the form of euphoric or manic mood swings, also need to be taken into account during chronic intake of glucocorticoids.

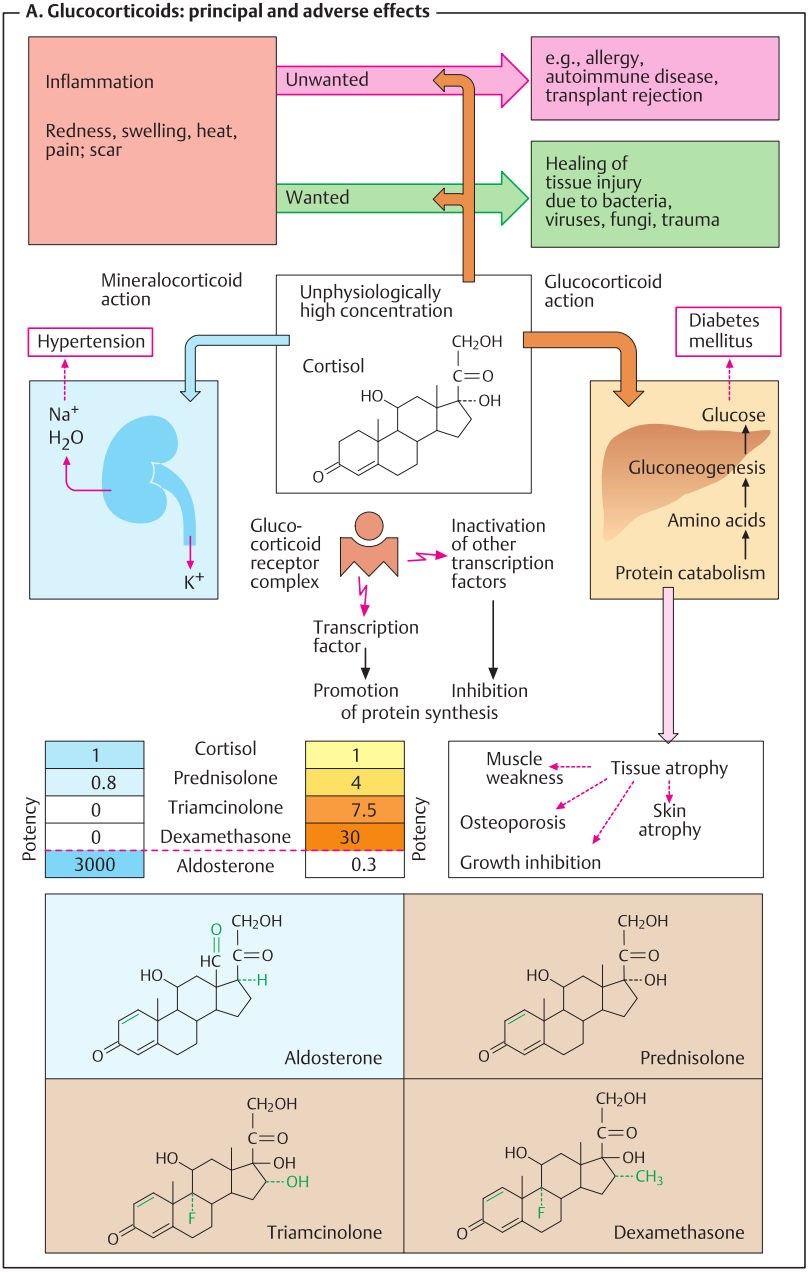

A. Glucocorticoids: principal and adverse effects
Inflammation
Redness, swelling, heat, pain; scar
Unwanted
Wanted
e.g., allergy, autoimmune disease, transplant rejection
Healing of tissue injury due to bacteria, viruses, fungi, trauma
Mineralocorticoid action
Unphysiologically high concentration
Glucocorticoid action
Hypertension
Cortisol
Diabetes mellitus
Na+
H2O
K+
Glucose
Gluconeogenesis
Amino acids
Protein catabolism
Gluco-corticoid receptor complex
Inactivation of other transcription factors
Transcription factor
Promotion of protein synthesis
Inhibition
Potency
1 Cortisol 1
0.8 Prednisolone 4
0 Triamcinolone 7.5
0 Dexamethasone 30
3000 Aldosterone 0.3
Potency
Muscle weakness
Tissue atrophy
Osteoporosis
Skin atrophy
Growth inhibition
Aldosterone
Prednisolone
Triamcinolone
Dexamethasone

Fig. 29.4

► **Measures for attenuating or preventing drug-induced Cushing syndrome.**

a) *Use of cortisol derivatives with less* (e.g., prednisolone) or *negligible mineralocorticoid activity* (e.g., triamcinolone, dexamethasone). Glucocorticoid activity of these congeners is increased. Glucocorticoid, anti-inflammatory, and feedback-inhibitory actions on the hypophysis are correlated. An exclusively anti-inflammatory congener does not exist. The "glucocorticoid"-related Cushing-like symptoms cannot be avoided. ► Fig. 29.5A lists relative activity (potency) with reference to cortisol, whose mineralocorticoid and glucocorticoid activities are assigned a value of 1.0. All listed glucocorticoids are effective orally.

b) *Local application.* This enables therapeutically effective concentrations to be built up at the site of application without a corresponding systemic exposure. Glucocorticoids subject to rapid biotransformation and inactivation following diffusion from the site of action are the preferred choice. Thus, inhalational administration employs glucocorticoids with a high presystemic elimination such as beclomethasone dipropionate, budesonide, flunisolide, or fluticasone propionate (p. 34). Adverse effects, however, also occur locally: e.g., via inhalation, oropharyngeal candidiasis (uninhibited *Candida* growth due to local immunosuppression) and hoarseness (probably due to damage to the vocal cord muscle); with cutaneous use, skin atrophy, striae, telangiectasias, and steroid acne; and with ocular use, cataracts and increased intraocular pressure (glaucoma).

c) *Lowest dosage possible.* For long-term medication, a just-sufficient dose should be given.

► **Effect of glucocorticoid administration on adrenocortical cortisol production (► Fig. 29.5A).** In both in the hypophysis and hypothalamus there are cortisol receptors through which cortisol can exert a feedback inhibition of release of regulatory hormones (ACTH and CRH). By means of these cortisol "sensors," the regulatory centers can monitor whether the actual blood level of the hormone corresponds to the "set-point." If the blood level exceeds the set-point, ACTH output is decreased and thus also the cortisol production. In this way, cortisol level is maintained within the required range. The regulatory centers respond to synthetic glucocorticoids as they do to cortisol. Administration of exogenous cortisol or any other glucocorticoid reduces the amount of endogenous cortisol needed to maintain homeostasis. Release of CRH and ACTH declines ("inhibition of higher centers by exogenous glucocorticoid") and, hence, cortisol secretion ("adrenocortical suppression"). After weeks of exposure to unphysiologically high glucocorticoid doses, the cortisol-producing portions of the adrenal cortex shrink ("adrenocortical atrophy"). Aldosterone-synthesizing capacity remains unaffected, however. If glucocorticoid medication is suddenly withheld, the atrophic cortex is unable to produce sufficient cortisol and a potentially life-threatening cortisol deficiency may develop. Therefore, glucocorticoid therapy should always be gradually reduced.

► **Regimens for prevention of adrenocortical atrophy.** Cortisol secretion is high in the early morning and low in the late evening (circadian rhythm). Accordingly, sensitivity to feedback inhibition must be high in the late evening. If adrenocortical atrophy has occurred or if full cortisol synthesis capacity (10-fold increase of the resting level during stress) has not yet been achieved after gradual weaning, a glucocorticoid must be given to cover severe physical stress (e.g., major surgery).

a) *Circadian administration:* The daily dose of glucocorticoid is given in the morning. Endogenous cortisol production will already have begun, the regulatory centers being relatively insensitive to inhibition. In the early morning hours of the next day, CRF/ACTH release and adrenocortical stimulation will resume.

b) *Alternate day therapy:* Twice the daily dose is given on alternate mornings. On the "off day," endogenous cortisol production is allowed to occur.

The disadvantage with either regimen is a recrudescence of disease symptoms during the glucocorticoid-free interval.

A. Cortisol release and its modification by glucocorticoids

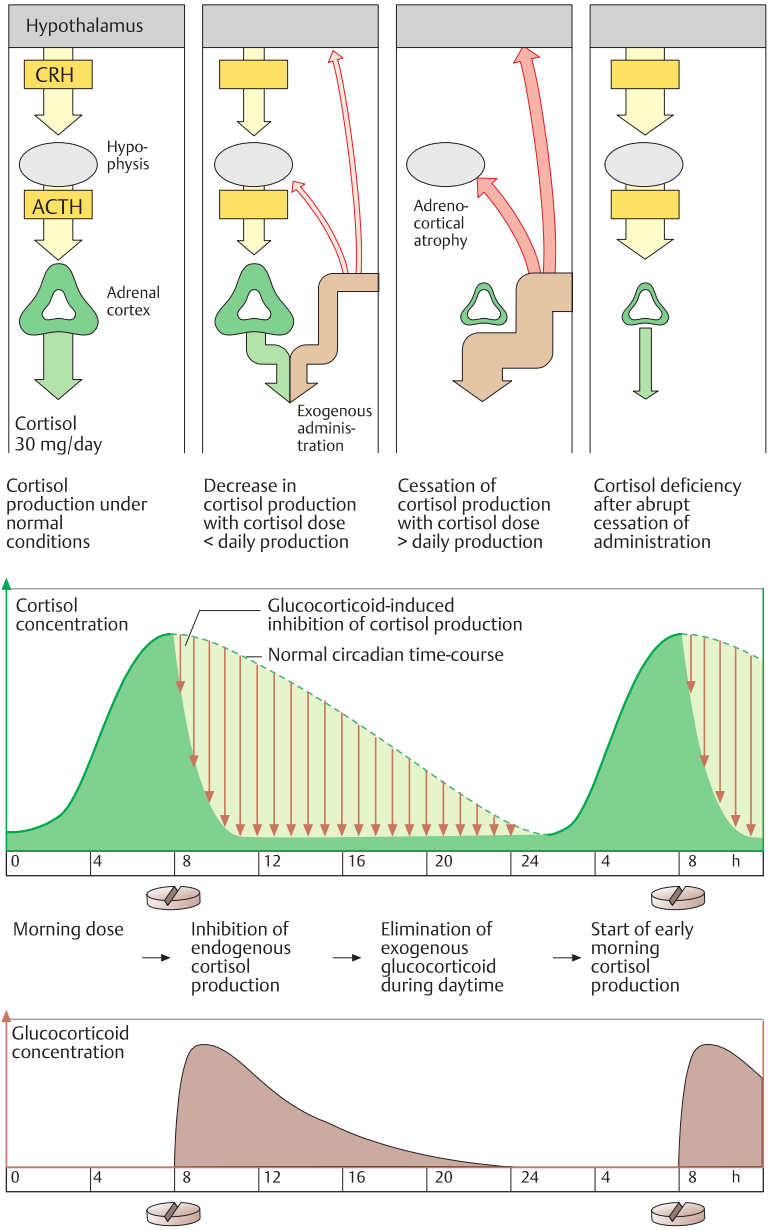


Fig. 29.5

Androgens, Anabolic Steroids, Antiandrogens

Androgens are masculinizing substances. The endogenous male gonadal hormone is the steroid **testosterone** from the interstitial Leydig cells of the testis. Testosterone secretion is stimulated by hypophyseal luteinizing hormone (LH), whose release is controlled by hypothalamic GnRH (gonadorelin, p. 236). Release of both hormones is subject to feedback inhibition by circulating testosterone. Reduction of testosterone to dihydrotestosterone (DHT) occurs in most target organs (e.g., the prostate gland); the latter possesses higher affinity for androgen receptors. In osteoblasts, testosterone is converted to estradiol by aromatase (p. 254), which promotes bone development. Rapid intrahepatic degradation of testosterone (plasma $t_{1/2}$ ~ 15 minutes) yields androsterone among other metabolites (17-ketosteroids) that are eliminated as conjugates in the urine. Because of rapid hepatic metabolism, testosterone is unsuitable for oral use.

► **Testosterone derivatives for clinical use.** Because of its good tissue penetrability, testosterone is well suited for percutaneous administration. Testosterone-heptanoate (or enanthate) is a testosterone ester for i.m. depot injection. It is given in oily solution by deep intramuscular injection. Upon diffusion of the ester from the depot, esterases quickly split off the acyl residue to yield free testosterone. A testosterone *ester for oral use is the undecanoate.* Owing to the fatty acid nature of undecanoic acid, this ester is absorbed into the lymph, enabling it to bypass the liver and enter the general circulation via the thoracic duct.

Indication: for hormone replacement in deficiency of endogenous testosterone production.

Anabolics are testosterone derivatives (e.g., clostebol, metenolone, nandrolone, stanozolol) that are used in debilitated patients, and are misused by athletes as doping agents, because of their protein anabolic effect. They act via stimulation of androgen receptors and, thus, also display androgenic actions (e.g., virilization in females, suppression of spermatogenesis).

Inhibitory Principles

GnRH superagonists (p. 236), such as buserelin, leuprorelin, and other "relins," are used in patients with metastasizing prostate cancer to inhibit production of testosterone which promotes tumor growth. Following transient stimulation, gonadotropin release subsides within a few days and testosterone levels fall as low as after surgical removal of the testes. **GnRH antagonists** "get right to the point" by blocking the receptors directly: abarelix and degarelix are examples.

► **Androgen receptor antagonists.** The antiandrogen *cyproterone* is a competitive antagonist of testosterone. By virtue of an additional progestin action, it decreases secretion of gonadotropins. *Indications:* in the male, dampening of sexual drive in hypersexuality, prostatic cancer; in the female, treatment of virilization phenomena, if necessary, with concomitant utilization of the progestagen contraceptive effect.

Flutamide (3 times a day) and *bicalutamide* and *enzalutamide* (each once a day) are structurally different androgen receptor antagonists lacking progestin activity.

► **5α-Reductase inhibition. Finasteride** and **dutasteride** inhibit 5α-reductase, reducing androgenic stimulation in those tissues where DHT is the active species (e.g., the prostate, hair follicles). Testosterone-dependent tissues and functions are not or hardly affected: e.g., skeletal musculature, feedback inhibition of gonadotropin release, or libido. Both can be used in benign prostatic hyperplasia to shrink the gland and to improve micturition.

At low p.o. dosage, finasteride may be offered to young men to counteract baldness.

► **Inhibition of androgen synthesis.** *Abiraterone* blocks testosterone synthesis by inhibiting CYP17-dependent 17α-hydroxylase/C17,20-lyase. It is used in the treatment of "castration-resistant" metastatic prostate cancer.

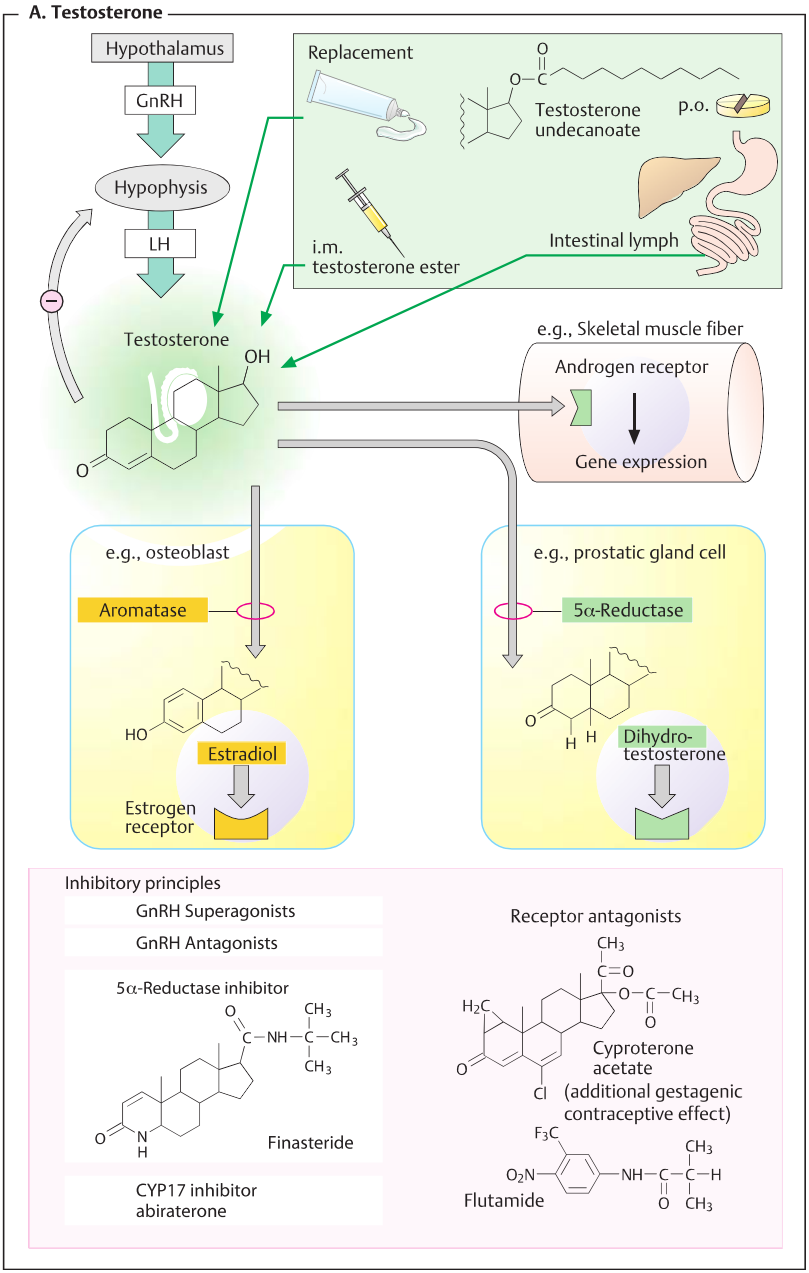

A. Testosterone
Hypothalamus
GnRH
Hypophysis
LH
Testosterone
OH
O
Replacement
Testosterone undecanoate
p.o.
i.m. testosterone ester
Intestinal lymph
e.g., Skeletal muscle fiber
Androgen receptor
Gene expression
e.g., osteoblast
Aromatase
HO
Estradiol
Estrogen receptor
e.g., prostatic gland cell
5α-Reductase
Dihydro-testosterone
Inhibitory principles
GnRH Superagonists
GnRH Antagonists
5α-Reductase inhibitor
Finasteride
CYP17 inhibitor abiraterone
Receptor antagonists
Cyproterone acetate
(additional gestagenic contraceptive effect)
Flutamide

Fig. 29.6

Follicular Growth and Ovulation, Estrogen and Progestin Production

Follicular maturation and ovulation, as well as the associated production of female gonadal hormones, are controlled by the hypophyseal gonadotropins FSH (follicle-stimulating hormone) and LH (luteinizing hormone). In the first half of the menstrual cycle, FSH promotes growth and maturation of ovarian tertiary follicles that respond with accelerating synthesis of estradiol. Estradiol stimulates endometrial growth and increases the permeability of cervical mucus for sperm cells. When the estradiol blood level approaches a predetermined set-point, FSH release is inhibited owing to feedback action on the anterior hypophysis. Since follicle growth and estrogen production are correlated, hypophysis and hypothalamus can "monitor" the follicular phase of the ovarian cycle through their estrogen receptors. Immediately prior to ovulation, when the nearly mature tertiary follicles are producing a high concentration of estradiol, the control loop switches to positive feedback. LH secretion transiently surges to peak levels and triggers ovulation. Within hours after ovulation, the tertiary follicle develops into the corpus luteum, which then also releases progesterone in response to LH. This initiates the secretory phase of the endometrial cycle and lowers the permeability of cervical mucus. Nonruptured follicles continue to release estradiol under the influence of FSH. After two weeks, production of progesterone and estradiol subsides, causing the secretory endometrial layer to be shed (menstruation).

The natural hormones are unsuitable for oral administration because they are subject to presystemic hepatic elimination. Estradiol is converted via estrone to estriol; by conjugation, all three can be rendered water-soluble and amenable to renal excretion. The major metabolite of progesterone is pregnanediol, which is also conjugated and eliminated renally.

► **Estrogen preparations. Depot preparations for i.m. injection** are oily solutions of esters of estradiol (3- or 17-OH group). The hydrophobicity of the acyl moiety determines the rate of absorption, hence the duration of effect. Released ester is hydrolyzed to yield free estradiol. Transdermal preparations utilize estradiol's good skin penetration.

► **Orally used preparations.** *Ethinylestradiol* (EE) is more stable metabolically, passes the liver after oral intake and mimics estradiol at estrogen receptors. In oral contraceptives, it forms the estrogen component (p. 250). *(Sulfate-) Conjugated estrogens* (excretory products) can be extracted from equine urine, have weak activity, and are used in the therapy of climacteric complaints. Their effectiveness is a matter of debate. Estradiol **transdermal delivery systems** are available.

► **Progestin preparations. Depot formulations for i.m. injection** are *17-α-hydroxyprogesterone caproate* and *medroxyprogesterone acetate*. **Preparations for oral use** are derivatives of ethinyltestosterone = ethisterone (e.g., norethisterone, dimethisterone, lynestrenol, desogestrel, gestodene), or of 17α-hydroxyprogesterone acetate (e.g., chlormadinone acetate or cyproterone acetate).

Indications for estrogens and progestins include hormonal contraception (p. 250); hormone replacement, as in postmenopausal women for prophylaxis of osteoporosis; bleeding anomalies; menstrual and severe climacteric complaints.

► **Adverse effects.** After long-term intake of estrogen/progestin preparations, increased risks have been reported for breast cancer, coronary heart disease, stroke, and thromboembolism. Although the incidence of bone fractures also decreases, the risk–benefit relationship is unfavorable. Concerning the adverse effects of oral contraceptives, see p. 250.

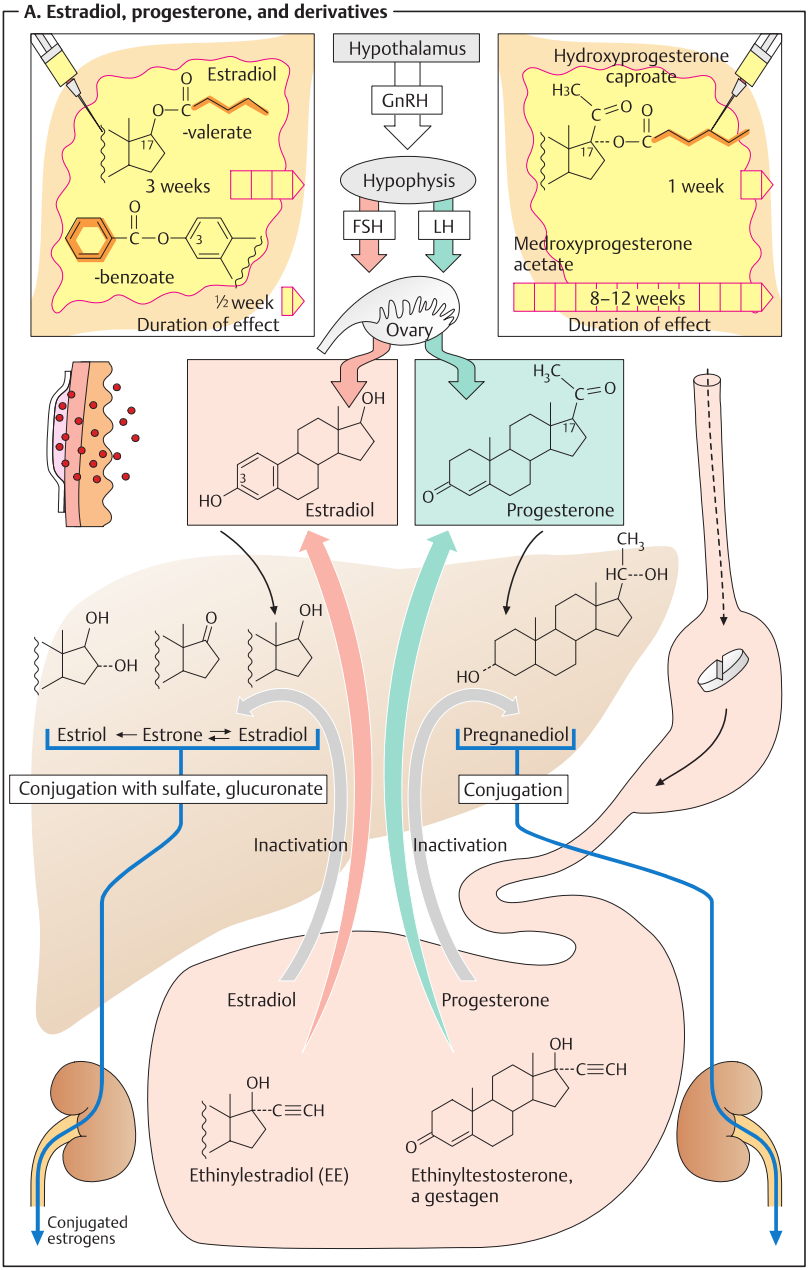

A. Estradiol, progesterone, and derivatives
Estradiol
-valerate
3 weeks
-benzoate
½ week
Duration of effect
Hypothalamus
GnRH
Hypophysis
FSH
LH
Ovary
Hydroxyprogesterone caproate
1 week
Medroxyprogesterone acetate
8–12 weeks
Duration of effect
Estradiol
Progesterone
Estriol ← Estrone ⇄ Estradiol
Conjugation with sulfate, glucuronate
Pregnanediol
Conjugation
Inactivation
Inactivation
Estradiol
Progesterone
Ethinylestradiol (EE)
Ethinyltestosterone, a gestagen
Conjugated estrogens

Fig. 29.7

Oral Contraceptives

► **Inhibitors of ovulation.** Negative feedback control of gonadotropin release can be utilized to inhibit the ovarian cycle. **Administration of exogenous estrogens** (usually ethinylestradiol on account of its good bioavailability when given orally) during the first half of the cycle permits **FSH production** to be suppressed (as it is by administration of progestins alone). Owing to the reduced FSH stimulation of tertiary follicles, **maturation of follicles and hence ovulation are prevented.** If estrogens alone are given during the first half of the cycle, endometrial and cervical responses, as well as other functional changes, will occur in the normal fashion. By adding a progestin (p. 248) during the second half of the cycle, the secretory phase of the endometrium and associated effects can be elicited. Discontinuation of hormone administration would be followed by menstruation.

The physiological time course of estrogen–progesterone release is simulated in the so-called **biphasic (sequential) preparations** (► Fig. 29.8A). **In monophasic preparations,** estrogen and progestin are taken concurrently. Early administration of progestin reinforces the inhibition of CNS regulatory mechanisms, prevents both normal endometrial growth and conditions for ovum implantation, and decreases penetrability of cervical mucus to sperm cells. The two latter effects also act to prevent conception. According to the staging of progestin administration, one distinguishes (► Fig. 29.8A): one-, two-, and three-stage preparations. Even with one-stage preparations, "withdrawal bleeding" occurs when hormone intake is discontinued (if necessary, by substituting dummy tablets).

► **Unwanted effects.** An increased risk of thromboembolism is attributed to the estrogen component in particular but is also associated with certain progestins (gestodene and desogestrel). The risk of myocardial infarction, stroke, and benign liver tumors is elevated. Nonetheless, the absolute prevalence of these events is low. Predisposing factors (family history, cigarette smoking, obesity, and age) have to be taken into account. The overall risk of malignant tumors does not appear to be increased. In addition, hypertension, fluid retention, cholestasis, nausea, and chest pain, are reported.

► **Minipill.** Continuous low-dose administration of progestin alone can prevent pregnancy. Ovulations are not suppressed regularly; the effect is then due to progestin-induced alterations in cervical and endometrial function. Because of the need for constant intake at the same time of day, a lower success rate, and relatively frequent bleeding anomalies, these preparations are now rarely employed.

► **"Morning-after" pill.** This refers to administration of a progestin (e.g., levonorgestrel) in high dosage up to 3 days after coitus. The mechanism of pregnancy prevention is still somewhat unclear. If the progestin acts prior to ovulation, it suppresses the ovulation-induced rise in LH (p. 248). Nausea and vomiting are frequent side effects.

► **Stimulation of ovulation. Gonadotropin secretion** can be increased by *pulsatile delivery of GnRH* (p. 236). Regarding clomifene (see p. 52), whereas this substance can be given orally, the gonadotropins presented below must be given parenterally. HMG is human menopausal gonadotropin extracted from the urine of postmenopausal women. Owing to the cessation of ovarian function, gonadotropins show elevated blood levels and pass into urine in utilizable quantities. HMG (menotropin) consists of FSH and LH. HCG is human chorionic gonadotropin; it is obtained from the urine of pregnant women and acts like LH. Recombinant FSH (follitropin) and LH are available. Corifollitropin α is a long-acting FSH analogue.

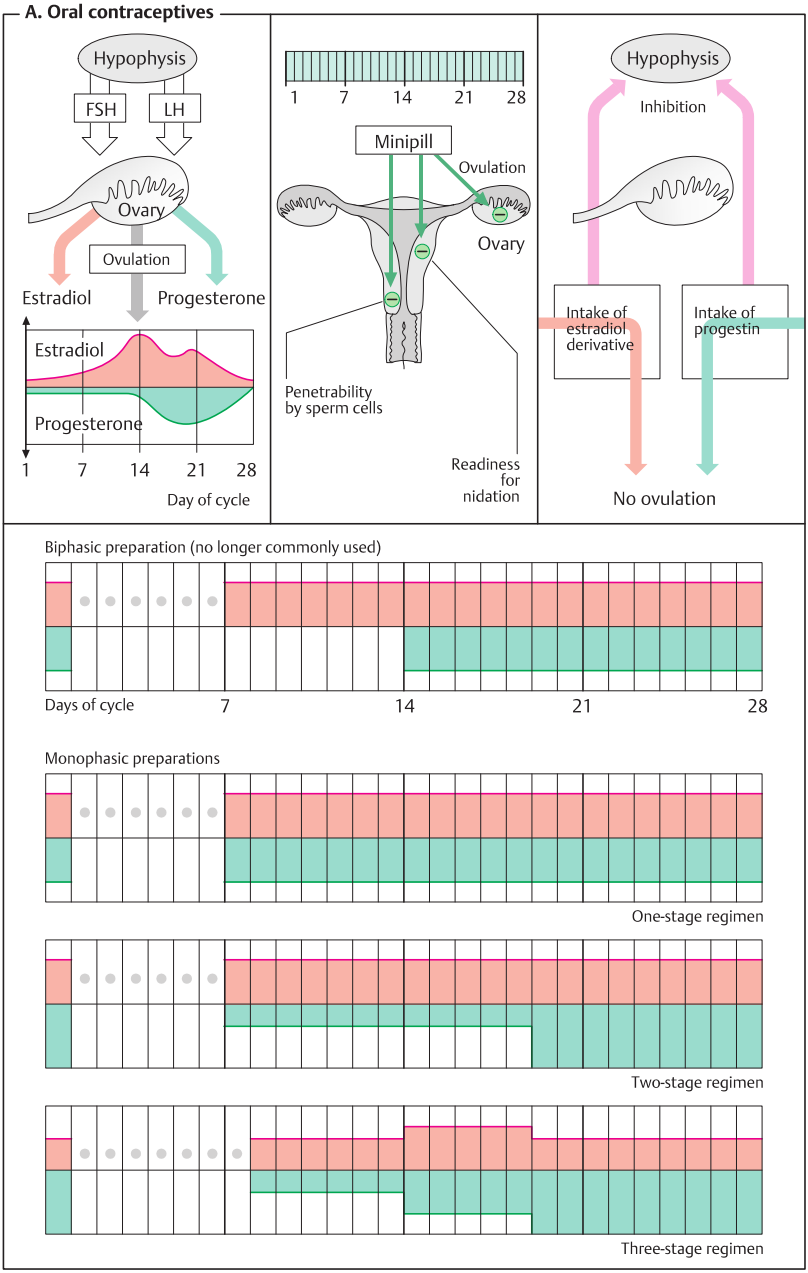

A. Oral contraceptives
Hypophysis
FSH
LH
Ovary
Ovulation
Estradiol
Progesterone
Estradiol
Progesterone
1
7
14
21
28
Day of cycle
1
7
14
21
28
Minipill
Ovulation
Ovary
Penetrability by sperm cells
Readiness for nidation
Hypophysis
Inhibition
Intake of estradiol derivative
Intake of progestin
No ovulation
Biphasic preparation (no longer commonly used)
Days of cycle
7
14
21
28
Monophasic preparations
One-stage regimen
Two-stage regimen
Three-stage regimen

Fig. 29.8

Antiestrogen and Antiprogestin Active Principles

► **Selective estrogen receptor modulators (SERMs) (► Fig. 29.9A).** Estrogen receptors belong to the group of transcription-regulating receptors (p. 82). The female gonadal hormone estradiol is an agonist at these receptors. Several drugs are available that can produce estrogen-antagonistic effects. Interestingly, these are associated with estrogen-agonistic effects in certain tissues. A tentative explanation derives from the idea that each ligand induces a specific conformation of the estrogen receptor. The ligand–estrogen receptor complexes combine with coactivators or repressors at specified gene sequences. The pattern of coregulators differs from tissue to tissue, allowing each SERM to generate a tissue-specific activity. It is of therapeutic significance that the patterns of estrogenic and antiestrogenic effects differ in a substance-specific manner among the drugs of this class.

It is useful to compare the activity profile of a SERM with that of estradiol, particularly in relation to effects seen postmenopausally. During chronic administration of estradiol, the risk of endometrial cancer rises; coadministration of a progestin prevents this effect. Breast cancers occur more frequently, likewise thromboembolic diseases. Estradiol effectively alleviates climacteric hot flashes and sweating. After chronic treatment it reduces the incidence of osteoporotic bone fractures by preventing the loss of an estrogen-dependent portion of bone mass (p. 348). Nonetheless, estrogens can no longer be recommended for this purpose because of the unfavorable benefit–risk constellation.

Clomifene is a stilbene derivative used orally for the therapy of female infertility. Owing to its antagonistic action at estrogen receptors in the adenohypophysis, feedback inhibition by estradiol of gonadotropin secretion is suppressed. The resulting increase in release of FSH induces augmented maturation of oocyte follicles. For instance, clomifene can be used for the treatment of luteal phase defects associated with disturbances of follicular maturation or the treatment of polycystic ovary syndrome. Since its use is confined to a few selected days during the ovarian cycle, chronic effects need not be considered.

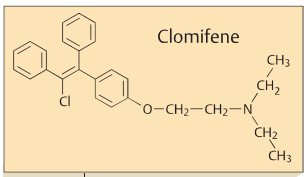
Tamoxifen is a stilbene derivative that is used in metastasizing breast cancer to block the estrogenic stimulus for tumor cell growth. As a mixed estrogenic antagonist / partial agonist, tamoxifen promotes rather than ameliorates climacteric complaints; at the same time it displays agonistic features that are of concern as a potential risk factor when use of the drug for the prophylaxis of breast cancer is being considered.

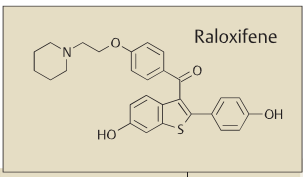
Raloxifene is approved for use in the treatment and prophylaxis of osteoporosis. As shown in the table opposite, it has other beneficial as well as adverse effects. Other SERMs on the market for the same indication are *lasofoxifene* and *bazedoxifene.*

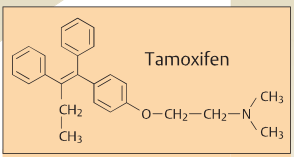
► **The estrogen receptor antagonist.** *Fulvestrant* is a reserve drug for treatment of hormone-dependent breast cancer.

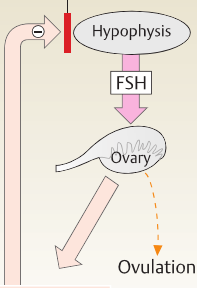
► **Progestin receptor antagonist (► Fig. 29.9B).** Approximately one week after conception, the embryo implants itself into the endometrium in the form of the blastocyst. By secreting human chorionic gonadotropin (HCG, mainly LH), the trophoblast maintains the corpus luteum and secretion of progesterone and thereby prevents menstrual bleeding. *Mifepristone* is an antagonist at progestin receptors and prevents maintenance of the endometrium during early pregnancy. Consequently, it acts as an abortifacient in early pregnancy. The **progestin receptor modulator** ulipristal acetate is used for emergency contraception within 5 days after unprotected intercourse.

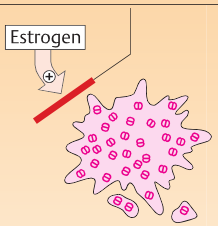
A. Selective estrogen receptor modulators (SERM)

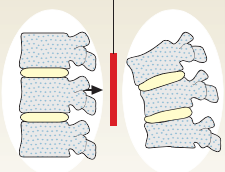








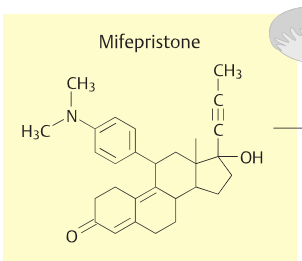




If no gestagen added

	Estradiol	Tamoxifen	Raloxifene
Endometrial cancer risk	↑	↑	↓
Breast cancer risk	↑	↓	↓
Thromboembolism	↑	↑	↑
Relief of climacteric complaints	↑	↓	↓
Bone mass	↑	↑	↑

B. Progestin receptor antagonist



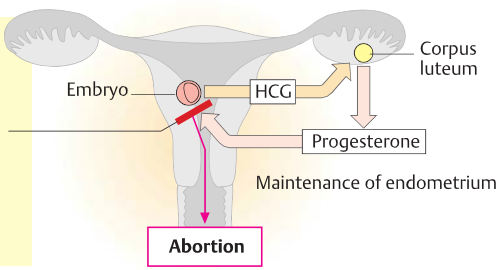


Fig. 29.9

Aromatase Inhibitors

Aromatase inhibitors constitute an additional antiestrogenic principle that is based upon inhibition of estrogen formation. They are used chiefly in the *therapy of advanced breast cancer* when the tumor has become insensitive to estrogen and the patient has completed menopause. However, one agent in this class (anastrozole) has been licensed for use in early breast cancer.

▶ **Aromatase.** The enzyme converts androgens such as testosterone and androstenedione into the estrogens estradiol and estrone. This reaction involves cleavage of the methyl group at C10 and aromatization of ring A. Aromatase is a cytochrome P450-containing enzyme (isozyme CYP19). During the female *reproductive phase,* the major portion of circulating estrogens originates from the ovaries, where estradiol is synthesized in the granulosa cells of the maturing tertiary follicles. Theca cells surrounding the granulosa cells supply androgen precursors. FSH stimulates formation of estrogens by inducing the synthesis of aromatase in granulosa cells. An isoform of the enzyme 17β-hydroxysteroid dehydrogenase (17β-HSD 1) catalyzes the conversion of androstenedione to testosterone and of estrone to estradiol. After menopause, *ovarian function* ceases. However, estrogens do not disappear completely from the blood because they continue to enter the circulation from certain other tissues, in particular the subcutaneous adipose tissue, which produces estrone. In hormone-dependent breast cancers, tumor growth is thereby promoted. In addition, breast cancer cells themselves may be capable of producing estrogens via aromatase.

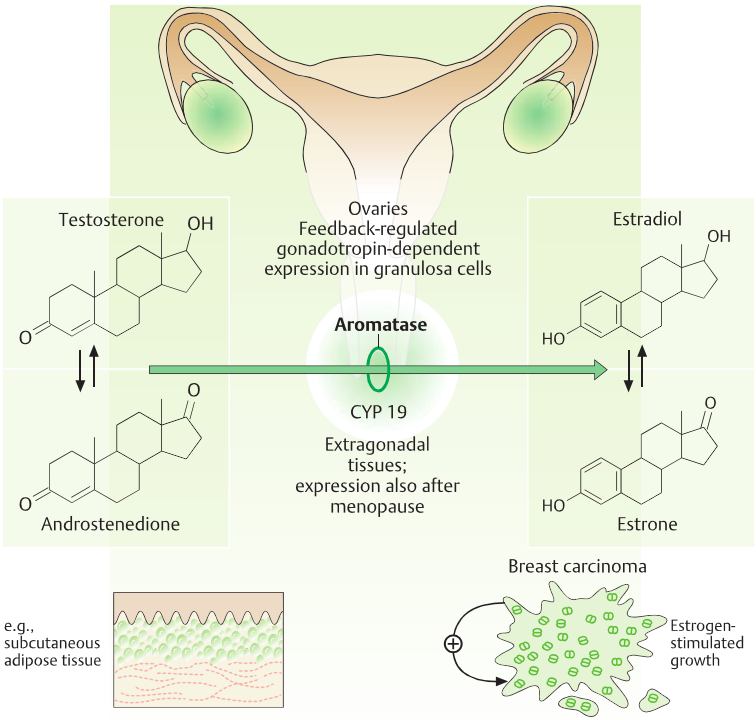
It should be noted that aromatase is also important in males. In osteoblasts it causes production of osteoanabolic estradiol from testosterone (p. 246).

▶ **Aromatase inhibitors** serve to eliminate extraovarian synthesis of estrogens in breast cancer patients. This can be achieved effectively only in postmenopause because, as an FSH-dependent enzyme, ovarian aromatase is subject to feedback regulation of female gonadal hormones. A drop in blood estradiol concentration would lead to increased release of FSH with a compensatory increase in synthesis of aromatase and estrogens.

Two groups of inhibitors can be distinguished on the basis of chemical structure and mechanism of action. *Steroidal inhibitors* (formestane, exemestane) attach to the androgen binding site on the enzyme and in the form of intermediary products give rise to an irreversible inhibition of the enzyme. *Nonsteroidal inhibitors* (anastrozole, letrozole) attach to a different binding site of the enzyme; via their triazole ring they interact reversibly with the heme iron of cytochrome P450.

Among the *adverse effects,* climacteric-like complaints predominate, reflecting the decline in estrogen levels. Unlike the SERMs, tamoxifen, which is used for the same indication, aromatase inhibitors do not promote endometrial growth and do not increase the risk of thromboembolic complications.

A. Aromatase inhibitors

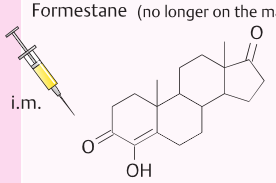


Inhibitors

Steroidal

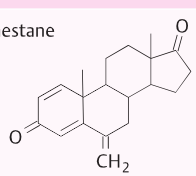
Formestane (no longer on the market)

i.m.



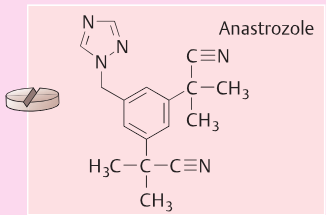
Exemestane

p.o.



Nonsteroidal

Anastrozole



Letrozole

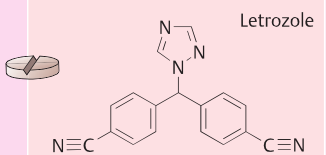


Fig. 29.10

Diabetes Mellitus

Diabetes mellitus develops when the influence of insulin on metabolism is inadequate. Type I diabetes is due to failure of B cells in the pancreas, while type II is due to insulin resistance of target cells, which cannot be overcome by an increase in insulin release.

► **Insulin formulations.** Insulin is synthesized in the B- (or β-) cells of the pancreatic islets of Langerhans. It is a protein (MW 5800) consisting of two peptide chains linked by two disulfide bridges; the A chain has 21 and the B chain 30 amino acids. Upon ingestion of carbohydrates, insulin is released into the blood, binds to its receptor (a ligand-activated tyrosine kinase [p. 82]), and promotes uptake and utilization of glucose in specific organs, namely, the heart, adipose tissue, and skeletal muscle.

Insulin is used in the **replacement therapy** of **diabetes mellitus.**

Human insulin (► Fig. 29.11**A**) can be produced in sufficient quantity by recombinant methods.

Recombinant insulin is produced to modify pharmacokinetic properties (see below). It is important in these insulin analogues that specificity for the insulin receptor is preserved, in particular relative to the receptor for IGF-1 = somatomedin C (p. 236), which promotes proliferation of cells.

► **Control of delivery from injection site into blood (► Fig. 29.11B).** As a peptide, insulin is unsuitable for oral administration. Usually, insulin preparations are injected subcutaneously. The duration of action depends on the rate of absorption from the injection site.

Variations in Dosage Form

► **Insulin solution.** Dissolved insulin is dispensed as a clear neutral solution known as regular (R) insulin or crystalline zinc insulin. In emergencies, such as hyperglycemic coma, it can be given intravenously (mostly by infusion because i.v. injections have too short an action; plasma $t_{1/2}$ ~9 minutes). With the usual subcutaneous administration, the effect is evident within 15–20 minutes, reaches a peak after ~3 hours, and lasts for ~6 hours.

► **Insulin suspensions.** When it is injected as a suspension of insulin-containing particles, dissolution and release of the hormone in subcutaneous tissue is retarded (**extended-action insulins**). Suitable particles can be obtained by precipitation of apolar, poorly water-soluble complexes consisting of anionic insulin and cationic partners, e.g., the polycationic protein protamine. In the presence of zinc ions, insulin crystallizes; crystal size determines the rate of dissolution. Intermediate-acting insulin preparations *(NPH* or *isophane; lente)* act for 18–26 hours, slow-acting preparations *(protamine zinc, ultralente)* for up to 36 hours.

Variation in Amino Acid Sequence

► **Rapidly acting insulin analogues.** After injection of a regular insulin solution, insulin molecules exist at the injection site in the form of hexameric aggregates. Only after disintegration into monomers can rapid diffusion into the bloodstream occur. In *insulin lispro,* two amino acids are exchanged, resulting in a diminished propensity toward aggregate formation. Thus, diffusion from the injection site is faster, with rapid onset and short duration of action. *Insulin aspart* and *insulin glulisine* have similar properties. Fast-acting insulins are injected immediately before a meal, whereas regular insulin requires a 15 to 30-minute interval between injection and food intake.

► **Long-acting insulin analogues.** The more extensive alteration of amino acids in *insulin glargine* changes the electric charge of the molecule. At pH 4 of the injectate, it is dissolved; however, at the pH of tissue it is poorly water-soluble and precipitates. Resolubilization and diffusion into the bloodstream take about one day. *Insulin detemir* has been modified by addition of a C_{14} fatty acid residue, which delays release from the injection site and promotes binding to albumin. It is used once or twice a day. *Insulin degludec* is similarly constructed with a C_{16} fatty acid residue and is used once a day.

Human insulin for inhalation has not become accepted by doctors and patients.

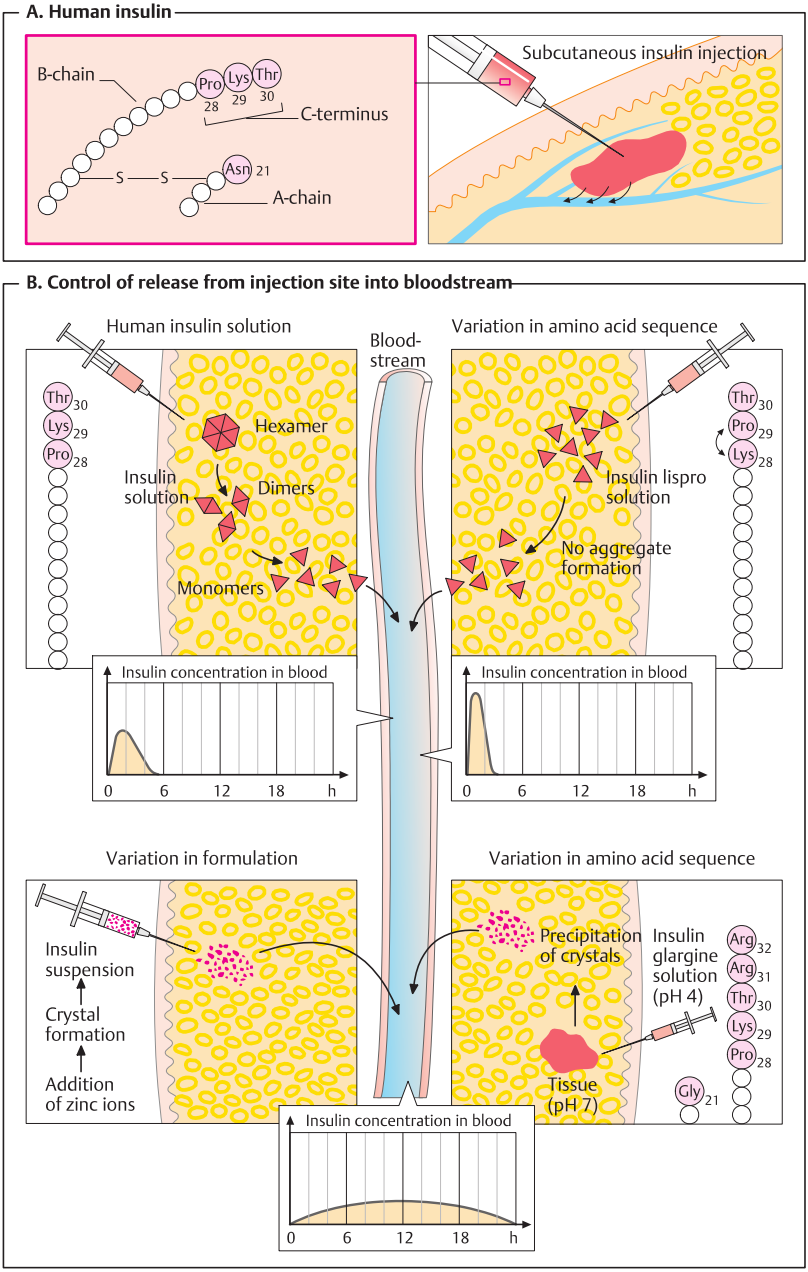

A. Human insulin
B-chain
Pro 28
Lys 29
Thr 30
C-terminus
S
S
Asn 21
A-chain
Subcutaneous insulin injection
B. Control of release from injection site into bloodstream
Human insulin solution
Blood-stream
Variation in amino acid sequence
Thr 30
Lys 29
Pro 28
Hexamer
Insulin solution
Dimers
Monomers
Insulin lispro solution
No aggregate formation
Pro 29
Lys 28
Insulin concentration in blood
0 6 12 18 h
Variation in formulation
Variation in amino acid sequence
Insulin suspension
Crystal formation
Addition of zinc ions
Precipitation of crystals
Insulin glargine solution (pH 4)
Arg 32
Arg 31
Thr 30
Lys 29
Pro 28
Gly 21
Tissue (pH 7)

Fig. 29.11

Treatment of Insulin-dependent Diabetes Mellitus

► **Pathogenesis and complications (► Fig. 29.12A).** Type I diabetes mellitus typically manifests in childhood or adolescence (juvenile onset diabetes mellitus); it is caused by the destruction of insulin-producing B cells in the pancreas. A genetic predisposition together with a precipitating factor (viral infection) could start an autoimmune reaction against B-cells. Replacement of insulin (daily dose ~40 U, equivalent to ~1.6 mg) becomes necessary.

Therapeutic objectives. (1) Prevention of life-threatening hyperglycemic (diabetic) coma; (2) prevention of diabetic sequelae arising from damage to small and large blood vessels, precise "titration" of the patient being essential to avoid even short-term spells of pathological hyperglycemia; (3) prevention of insulin overdosage leading to life-threatening hypoglycemic shock (CNS disturbance due to lack of glucose).

► **Therapeutic principles.** In healthy subjects, the amount of insulin is "automatically" matched to carbohydrate intake, hence to blood glucose concentration. The critical secretory stimulus is the rise in plasma glucose level. Food intake and physical activity (increased glucose uptake into musculature, decreased insulin demand) are accompanied by corresponding changes in insulin secretion.

► **Methods of insulin replacement (► Fig. 29.12B).** In the diabetic, insulin can be administered as it is normally secreted. For instance, administration of a long-acting insulin in the late evening generates a basal level, whereas a fast acting insulin is used before meals. The dose needed is determined on the basis of the actual blood glucose concentration measured by the patient and the meal-dependent demand. This regimen (so-called *intensified insulin therapy)* provides the patient with much flexibility in planning daily activities. A well-educated, cooperative, and competent patient is a precondition. In other cases, a fixed-dosage schedule *(conventional insulin therapy)* will be needed, e.g., with morning and evening injections of a combination insulin (a mixture of regular insulin plus insulin suspension) in constant respective dosage (► Fig. 29.12A). To avoid hypoglycemia or hyperglycemia, dietary carbohydrate (CH) intake must be synchronized with the time course of insulin absorption from the s.c. depot: diet control! Caloric intake is to be distributed (50% CH, 30% fat, 20% protein) in small meals over the day so as to achieve a steady CH supply—snacks, late night meal. Rapidly absorbable CH (sweets, cakes) must be avoided (hyperglycemic peaks) and replaced with slowly digestible ones.

Undesirable Effects

Hypoglycemia is heralded by warning signs: tachycardia, unrest, tremor, pallor, profuse sweating. Some of these are due to the release of glucose-mobilizing epinephrine. *Countermeasures:* glucose administration, rapidly absorbed CH orally (diabetics should always have a suitable preparation within reach) or 10–20 g glucose i.v. in case of unconsciousness; if necessary, injection of glucagon, the pancreatic hyperglycemic hormone.

Allergic reactions are rare; locally, redness may occur at the injection site and atrophy of adipose tissue; *lipodystrophy).* A possible local *lipohypertrophy* can be avoided by alternating injection sites.

Even with optimal control of blood sugar, s.c. administration of insulin cannot fully replicate the physiological situation (**C**). In healthy subjects, absorbed glucose and insulin released from the pancreas simultaneously reach the liver in high concentrations, whereby effective presystemic elimination of both substances is achieved. In the diabetic, s.c. injected insulin is uniformly distributed in the body. Since insulin concentration in blood supplying the liver cannot rise, less glucose is extracted from portal blood. A significant amount of glucose enters extrahepatic tissues, where it has to be utilized.

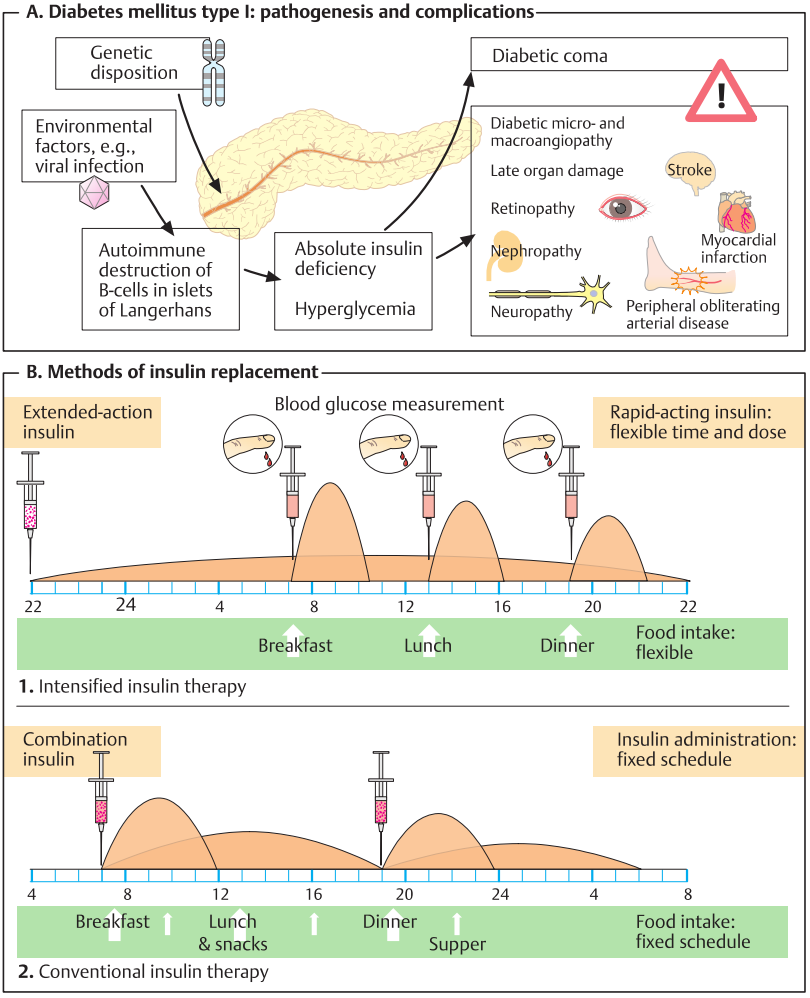

A. Diabetes mellitus type I: pathogenesis and complications
Genetic disposition
Environmental factors, e.g., viral infection
Autoimmune destruction of B-cells in islets of Langerhans
Absolute insulin deficiency
Hyperglycemia
Diabetic coma
Diabetic micro- and macroangiopathy
Late organ damage
Stroke
Retinopathy
Myocardial infarction
Nephropathy
Neuropathy
Peripheral obliterating arterial disease
B. Methods of insulin replacement
Extended-action insulin
Blood glucose measurement
Rapid-acting insulin: flexible time and dose
22
24
4
8
12
16
20
22
Breakfast
Lunch
Dinner
Food intake: flexible
1. Intensified insulin therapy
Combination insulin
Insulin administration: fixed schedule
4
8
12
16
20
24
4
8
Breakfast
Lunch & snacks
Dinner
Supper
Food intake: fixed schedule
2. Conventional insulin therapy
C. Presystemic and systemic insulin action in healthy and diabetic subjects
Insulin
Glucose
Healthy subject
Insulin
Diabetic

Fig. 29.12

Treatment of Type II Diabetes Mellitus

In this disease there is a relative insulin deficiency. In the past, type II diabetes typically occurred in overweight older adults. However, the term "maturity-onset diabetes" is no longer appropriate as the average age of disease onset has become earlier with the growing incidence of overweight children and adolescents.

The cause of **increased insulin requirement** is an **insulin resistance** of target organs. The decrease in the effectiveness of insulin is due to a reduction in the density of insulin receptors in target tissues and a decreased efficiency of signal transduction of insulin-receptor complexes. Conceivably, obesity with increased storage of triglycerides causes a decrease in insulin sensitivity of target organs. The loss in sensitivity can be compensated by enhancing insulin concentration. In ▶ Fig. 29.13**A**, this situation is represented schematically by the decreased receptor density. In the obese patient, the maximum binding possible (plateau of curve) is displaced downward, indicative of the reduction in receptor numbers. At low insulin concentrations, correspondingly less binding of insulin occurs, compared with the control condition (normal weight). For a given metabolic effect (say, utilization of carbohydrates contained in a piece of cake), a certain number of receptors must be occupied. As shown by the binding curves (dashed lines), this can still be achieved with a reduced receptor number; although only at a higher concentration of insulin.

▶ **Development of Type II diabetes mellitus** (▶ **Fig. 29.13B**). A subject with normal body weight (left) ingests a specified amount of carbohydrate; to maintain blood glucose concentration within the physiological range, the necessary amount of insulin is released into the blood. Compared with a normal subject, the overweight patient with insulin resistance requires a continually elevated output of insulin (orange curves) to avoid an excessive rise of blood glucose levels (green curves) during an equivalent carbohydrate load. When **the insulin secretory capacity of the pancreas decreases,** this is first noted as a rise in blood glucose during glucose loading (latent diabetes mellitus). As insulin secretory capacity declines further, not even the fasting blood level can be maintained (manifest, overt diabetes).

▶ **Treatment.** Caloric restriction to restore body weight to normal is associated with an increase in insulin responsiveness, even before a normal weight is reached. Moreover, physical activity is important because it enhances peripheral utilization of glucose. When changes in lifestyle are insufficient in correcting the diabetic condition, therapy with oral antidiabetics is indicated (p. 262). **Therapy of first choice is weight reduction, not administration of drugs!**

A metabolic syndrome is said to be present when at least three of the following five risk factors can be identified in a patient:

1. Elevated blood glucose levels
2. Elevated blood lipid levels
3. Obesity
4. Lowered HDL levels
5. Hypertension

Overweight and resistance to insulin appear to play pivotal roles in the pathophysiological process. The resulting hyperinsulinemia induces a rise in systemic arterial blood pressure and probably also a hyperglyceridemia associated with an unfavorable LDL/HDL quotient. This combination of risk factors lowers life expectancy and calls for therapeutic intervention. The metabolic syndrome has a high prevalence; in industrialized countries, up to 20% of adults are believed to suffer from it.

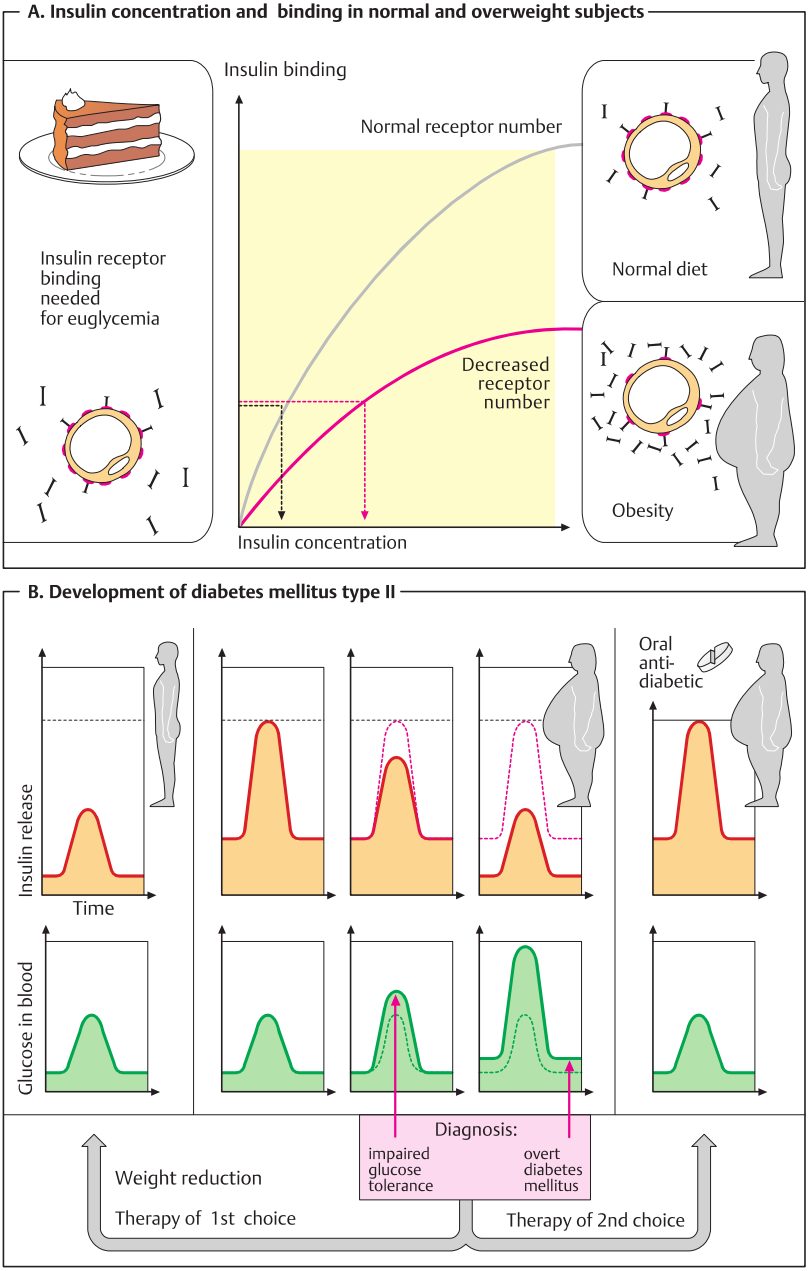

A. Insulin concentration and binding in normal and overweight subjects
Insulin receptor binding needed for euglycemia
Insulin binding
Normal receptor number
Decreased receptor number
Insulin concentration
Normal diet
Obesity
B. Development of diabetes mellitus type II
Insulin release
Time
Glucose in blood
Oral anti-diabetic
Diagnosis:
impaired glucose tolerance
overt diabetes mellitus
Weight reduction
Therapy of 1st choice
Therapy of 2nd choice

Fig. 29.13

Oral Antidiabetic Drugs

In principle, the blood concentration of glucose represents a balance between influx into the bloodstream (chiefly from liver and intestines) and egress from blood into consuming tissues and organs. In ▶ Fig. 29.14A, drugs available for lowering an elevated level of glucose are grouped schematically in relation to these two processes.

Metformin is a **biguanide derivative.** The mechanism underlying its blood glucose-lowering effect is not completely understood. Decreased glucose release from the liver appears to play an essential part. Metformin does not increase release of insulin. The risk of hypoglycemia is relatively less common. Metformin has proved itself as a monotherapeutic in obese type II diabetics. It can be combined with other oral antidiabetics as well as insulin. Frequent adverse effects include anorexia, nausea, and diarrhea. Overproduction of lactic acid (lactate acidosis) is a rare, potentially fatal reaction. It is contraindicated in renal insufficiency (accumulation) and in diseases associated with hypoxia (e.g., severe heart failure, respiratory failure) and therefore should be avoided in elderly patients.

Oral antidiabetics of the *sulfonylurea* type increase the release of insulin from pancreatic B cells. They inhibit *ATP-gated K^+ channels* and thereby cause depolarization of the B-cell membrane. Normally, these channels are closed when intracellular levels of glucose, and hence of ATP, increase. This drug class includes glibenclamide and glimepiride. In some patients, it is not possible to stimulate insulin secretion from the outset; in others, therapy fails later. Matching of dosage of the oral antidiabetic and caloric intake is necessary. Hypoglycemia is the most important unwanted effect. Enhancement of the hypoglycemic effect can result from drug interactions: displacement of antidiabetic drug from plasma protein binding sites, for example, by sulfonamides or acetylsalicylic acid.

Repaglinide and *nateglinide* possess the same mechanism of action as the sulfonylureas but differ in chemical structure. After oral administration, the effect develops rapidly and fades away quickly. Therefore, glinides can be taken immediately before a meal.

Incretin mimetics. Enteral delivery of glucose leads to greater insulin release than parenteral administration. The gut hormone glucagon-like peptide-1 (GLP-1) is one of the incretins and stimulates insulin release. It also delays gastric emptying and reduces appetite. *Exenatide, lixisenatide* and *liraglutide* are incretin analogues that are resistant to metabolism (direct incretin mimetics). *Sitagliptin, vildagliptin* and other "gliptins" inhibit a peptidase (dipeptidyl peptidase 4 or DPP4) that breaks down GLP-1 rapidly (indirect incretin mimetics).

"Glitazone" is an appellation referring to thiazolidinedione derivatives. These are agonists at the peroxisome proliferator-activated receptor of the γ-subtype (PPARγ), a transcription-regulating receptor. PPARγ has a role in many kinds of cells and so lacks specificity for treatment of type II diabetes. These drugs (a) promote the maturation of preadipocytes into adipocytes, (b) increase insulin sensitivity, and (c) enhance cellular glucose uptake. Besides fat tissue, skeletal muscle is also affected.

Adverse effects include weight gain and fluid retention, and congestive heart failure. An increased risk for myocardial infarction and bone fractures has been reported. *Pioglitazone* is the only glitazone still on the market in Germany.

Inhibition of renal reabsorption of glucose by *dapagliflozin*, *canagliflozin*, and *empagliflozin* is an interesting new approach for lowering the blood glucose level.

Acarbose is an inhibitor of α-glucosidase (localized in the brush border of intestinal epithelium), which liberates glucose from disaccharides. It *retards* breakdown of carbohydrates, and hence absorption of glucose. Owing to increased fermentation of carbohydrates by gut bacteria, flatulence and diarrhea may develop. Miglitol has a similar effect but is absorbed from the intestine.

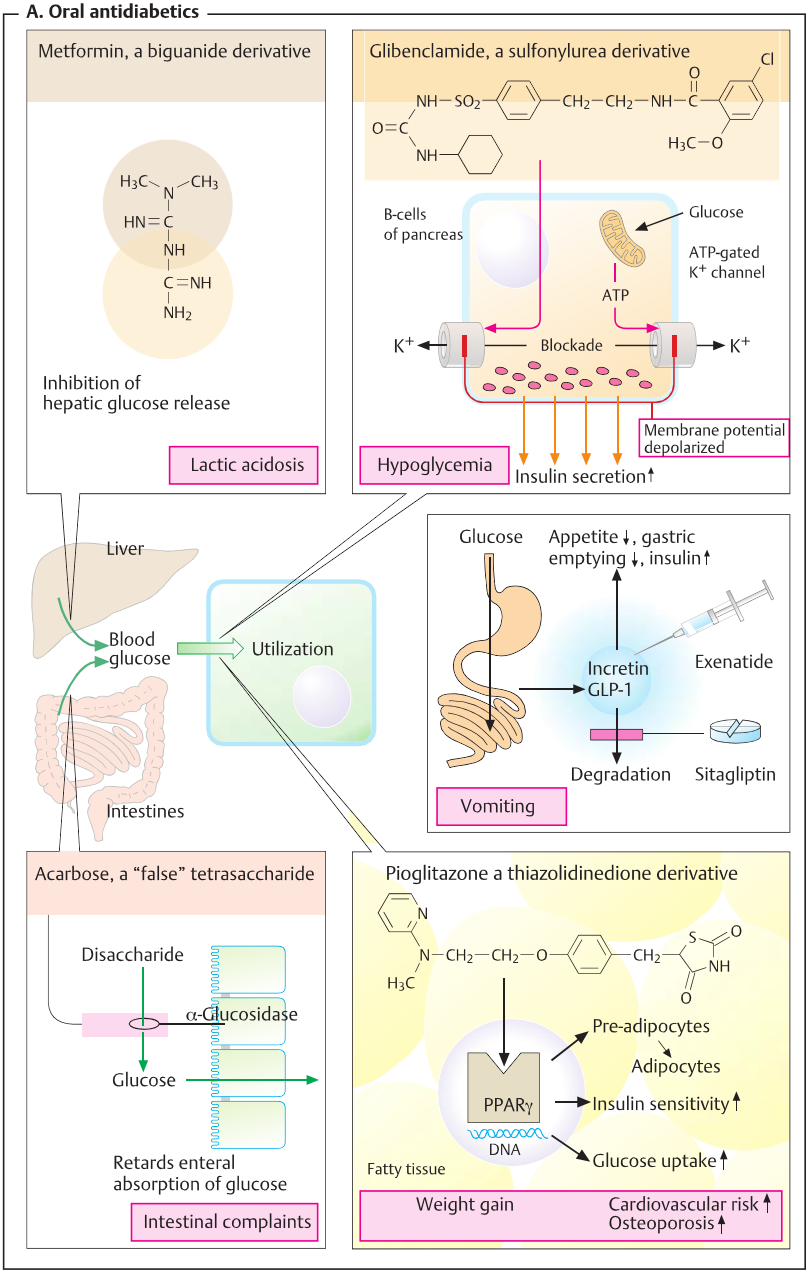

A. Oral antidiabetics
Metformin, a biguanide derivative
Inhibition of hepatic glucose release
Lactic acidosis
Glibenclamide, a sulfonylurea derivative
B-cells of pancreas
Glucose
ATP-gated K+ channel
ATP
K+
Blockade
K+
Membrane potential depolarized
Hypoglycemia
Insulin secretion
Liver
Blood glucose
Utilization
Intestines
Glucose
Appetite, gastric emptying, insulin
Incretin GLP-1
Exenatide
Degradation
Sitagliptin
Vomiting
Acarbose, a "false" tetrasaccharide
Disaccharide
α-Glucosidase
Glucose
Retards enteral absorption of glucose
Intestinal complaints
Pioglitazone a thiazolidinedione derivative
PPARγ
DNA
Pre-adipocytes
Adipocytes
Insulin sensitivity
Glucose uptake
Fatty tissue
Weight gain
Cardiovascular risk
Osteoporosis

Fig. 29.14

Drugs for Maintaining Calcium Homeostasis

At rest, the intracellular concentration of free calcium ions (Ca^{2+}) is kept at 0.1 µM (see p. 146 for mechanisms involved). During excitation, a transient rise of up to 10 µM elicits contraction in muscle cells (electromechanical coupling) and secretion in glandular cells (electrosecretory coupling). The cellular content of Ca^{2+} is in equilibrium with the extracellular Ca^{2+} concentration (1000 µM), as is the plasma protein-bound fraction of calcium in blood. Ca^{2+} may crystallize with phosphate to form hydroxyapatite, the mineral of bone. Osteoclasts are phagocytes that mobilize Ca^{2+} by resorption of bone. Slight changes in extracellular Ca^{2+} concentration can alter organ function: thus, excitability of skeletal muscle increases markedly as Ca^{2+} is lowered (e.g., in hyperventilation tetany). Three hormones are available to the body for maintaining a constant extracellular Ca^{2+} concentration.

Vitamin D hormone is derived from *vitamin D (cholecalciferol).* Vitamin D can also be produced in the body; it is formed in the skin from dehydrocholesterol during irradiation with UV light. When there is lack of solar radiation, dietary intake becomes essential, cod liver oil being a rich source. Metabolically active vitamin D hormone results from two successive hydroxylations: in the liver at position 25 (→ calcifediol) and in the kidney at position 1 (→ calcitriol = vitamin D hormone). 1-Hydroxylation depends on the level of calcium homeostasis and is stimulated by parathormone and a fall in plasma levels of Ca^{2+} and phosphate. Vitamin D hormone promotes enteral absorption and renal reabsorption of Ca^{2+} and phosphate. As a result of the increased Ca^{2+} and phosphate concentration in blood, there is an increased tendency for these ions to be deposited in bone in the form of hydroxyapatite crystals. In vitamin D deficiency, bone mineralization is inadequate (rickets, osteomalacia). **Therapeutic use** aims at *replacement.* Mostly, vitamin D is given; in liver disease, calcifediol may be indicated, in renal disease, calcitriol. **Overdosage** may induce hypercalcemia with deposits of calcium salts in tissues (particularly in kidney and blood vessels): calcinosis.

The polypeptide **parathormone** is released from the parathyroid glands when the plasma Ca^{2+} level falls. It *stimulates osteoclasts* to increase bone resorption; in the kidneys it promotes calcium reabsorption, while phosphate excretion is enhanced. As blood phosphate concentration diminishes, the tendency of Ca^{2+} to precipitate as bone mineral decreases. By stimulating the formation of vitamin D hormone, parathormone has an indirect effect on the enteral uptake of Ca^{2+} and phosphate. In parathormone deficiency, vitamin D can be used as a substitute that, unlike parathormone, is effective orally. *Teriparatide* is a recombinant shortened parathormone derivative containing the portion required for binding to the receptor. It can be used in the therapy of postmenopausal osteoporosis and promotes bone formation. While this effect seems paradoxical in comparison with hyperparathyroidism, it obviously arises from the special mode of administration: the once daily s.c. injection generates a quasi-pulsatile stimulation. The same can be achieved today by a once-daily parathormone injection. **Cinacalcet** halts the activity of the parathyroids by allosterically rendering their receptors more sensitive to extracellular Ca^{2+}. It can be used in the treatment of hyperparathyroidism.

The polypeptide **calcitonin** is secreted by thyroid C cells during imminent hypercalcemia. It lowers elevated plasma Ca^{2+} levels by *inhibiting osteoclast activity.* Its uses include hypercalcemia and osteoporosis. Remarkably, calcitonin injection may produce a sustained *analgesic* effect that alleviates pain associated with bone diseases (Paget disease, osteoporosis, neoplastic metastases) or complex regional pain (Sudeck) syndrome.

Hypercalcemia can be treated by (1) administering 0.9% NaCl solution plus furosemide (if necessary) → increased renal Ca^{2+}excretion; (2) the osteoclast inhibitors calcitonin and clodronate (a bisphosphonate) → decreased bone Ca^{2+} mobilization; (3) glucocorticoids.

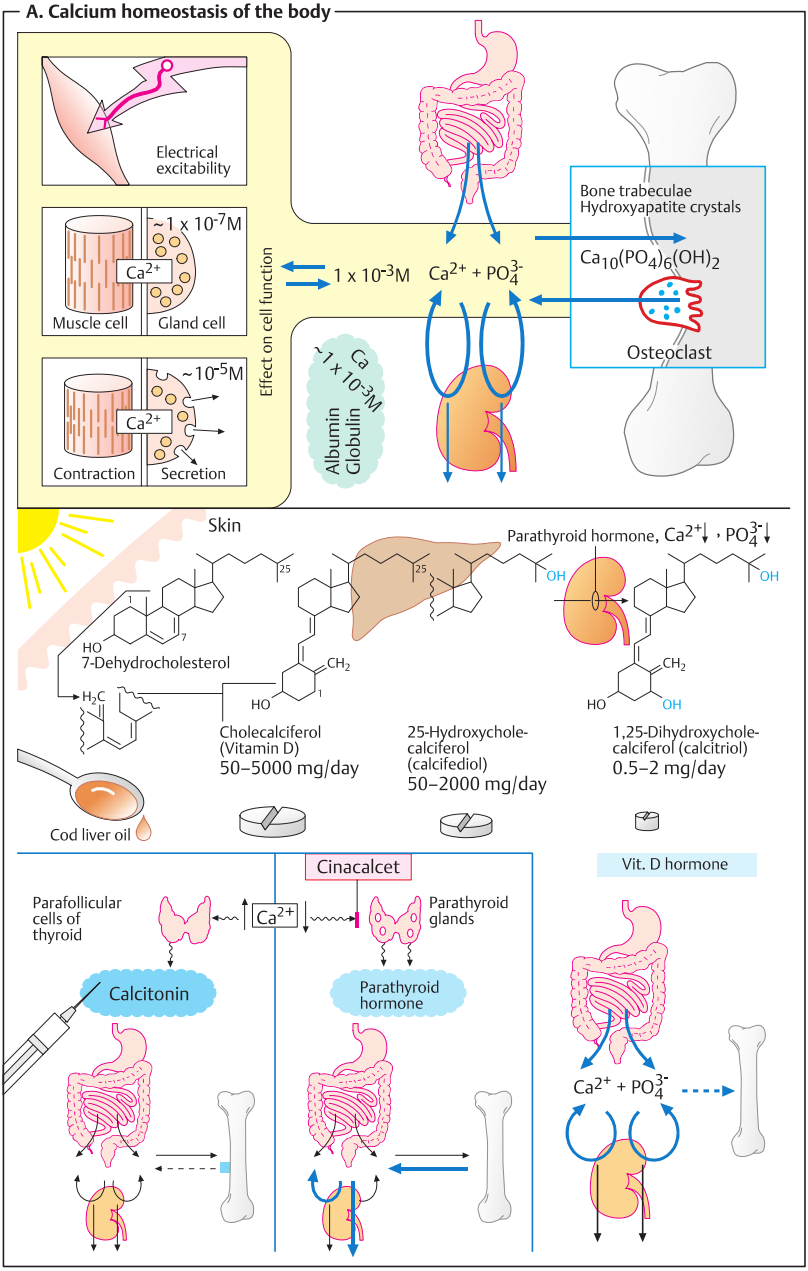

A. Calcium homeostasis of the body
Electrical excitability
~1 x 10-7M
Ca2+
Muscle cell
Gland cell
~10-5M
Ca2+
Contraction
Secretion
Effect on cell function
1 x 10-3M
Ca2+ + PO43-
Bone trabeculae
Hydroxyapatite crystals
Ca10(PO4)6(OH)2
Osteoclast
~1 x 10-3M
Ca
Albumin
Globulin
Skin
7-Dehydrocholesterol
Cholecalciferol
(Vitamin D)
50–5000 mg/day
Parathyroid hormone, Ca2+↓, PO43-↓
25-Hydroxychole-
calciferol
(calcifediol)
50–2000 mg/day
1,25-Dihydroxychole-
calciferol (calcitriol)
0.5–2 mg/day
Cod liver oil
Cinacalcet
Vit. D hormone
Parafollicular
cells of
thyroid
Ca2+
Parathyroid
glands
Calcitonin
Parathyroid
hormone
Ca2+ + PO43-

Fig. 29.15

Drugs for Treating Bacterial Infections

When bacteria overcome the cutaneous or mucosal barriers and penetrate into body tissues, a bacterial *infection* is present. Frequently the body succeeds in removing the invaders, without outward signs of disease, by mounting an immune response. However, certain pathogens have evolved a sophisticated counterstrategy. Although they are taken up into host cells via the regular phagocytic pathway, they are able to forestall the subsequent fusion of the phagosome with a lysosome and in this manner can escape degradation. Since the wall of the sheltering vacuole is permeable to nutrients (amino acids, sugars), the germs are able to grow and multiply until the cell dies and the released pathogens can infect new host cells. This strategy is utilized, e.g., by *Chlamydia* and *Salmonella* species, *Mycobacterium tuberculosis, Legionella pneumophila, Toxoplasma gondii,* and *Leishmania* species. It is easy to see that targeted pharmacotherapy is especially difficult in such cases because the drug cannot reach the pathogen until it has surmounted first the cell membrane and then the vacuolar membrane. If bacteria multiply faster than the body's defenses can destroy them, *infectious disease* develops, with inflammatory signs, e.g., purulent wound infection or urinary tract infection. Appropriate treatment employs substances that injure bacteria and thereby prevent their further multiplication, without harming cells of the host organism (▶ Fig. 30.11).

Specific damage to bacteria is particularly feasible when a substance interferes with a metabolic process that occurs in bacterial but not in host cells. Clearly this applies to inhibitors of cell wall synthesis, since human or animal cells lack a cell wall. The **points of attack of antibacterial agents** are schematically illustrated in a grossly simplified schematic of a bacterial cell, as depicted in ▶ Fig. 30.12.

The effect of antibacterial drugs can be observed in vitro (▶ Fig. 30.13). Bacteria multiply in a growth medium under controlled conditions. If the medium contains an antibacterial drug, two results can be discerned: (a) bacteria are killed**—bactericidal effect;** or (b) bacteria survive, but do not multiply**—bacteriostatic effect.** Although variations may occur under therapeutic conditions, the different drugs can be classified according to their primary mode of action (color tone in ▶ Fig. 30.12).

When bacterial growth remains unaffected by an antibacterial drug, bacterial **resistance** is present. This may occur because of certain metabolic characteristics that confer a natural insensitivity to the drug on a particular strain of bacteria *(natural resistance).* Depending on whether a drug affects only few or numerous types of bacteria, the terms **narrow-spectrum** (e.g., penicillin G) or **broad-spectrum** (e.g., tetracyclines) **antibiotic** are applied. Naturally susceptible bacterial strains can be transformed under the influence of antibacterial drugs into resistant ones *(acquired resistance),* when a random genetic alteration (mutation) gives rise to a resistant bacterium. Under the influence of the drug, the susceptible bacteria die off, whereas the mutant multiplies unimpeded. The more frequently a given drug is administered, the more probable the emergence of resistant strains (e.g., hospital strains with multiple resistance)!

Resistance can also be acquired when DNA responsible for nonsusceptibility (so-called *resistance plasmid)* is passed on from other resistant bacteria by conjugation or transduction.

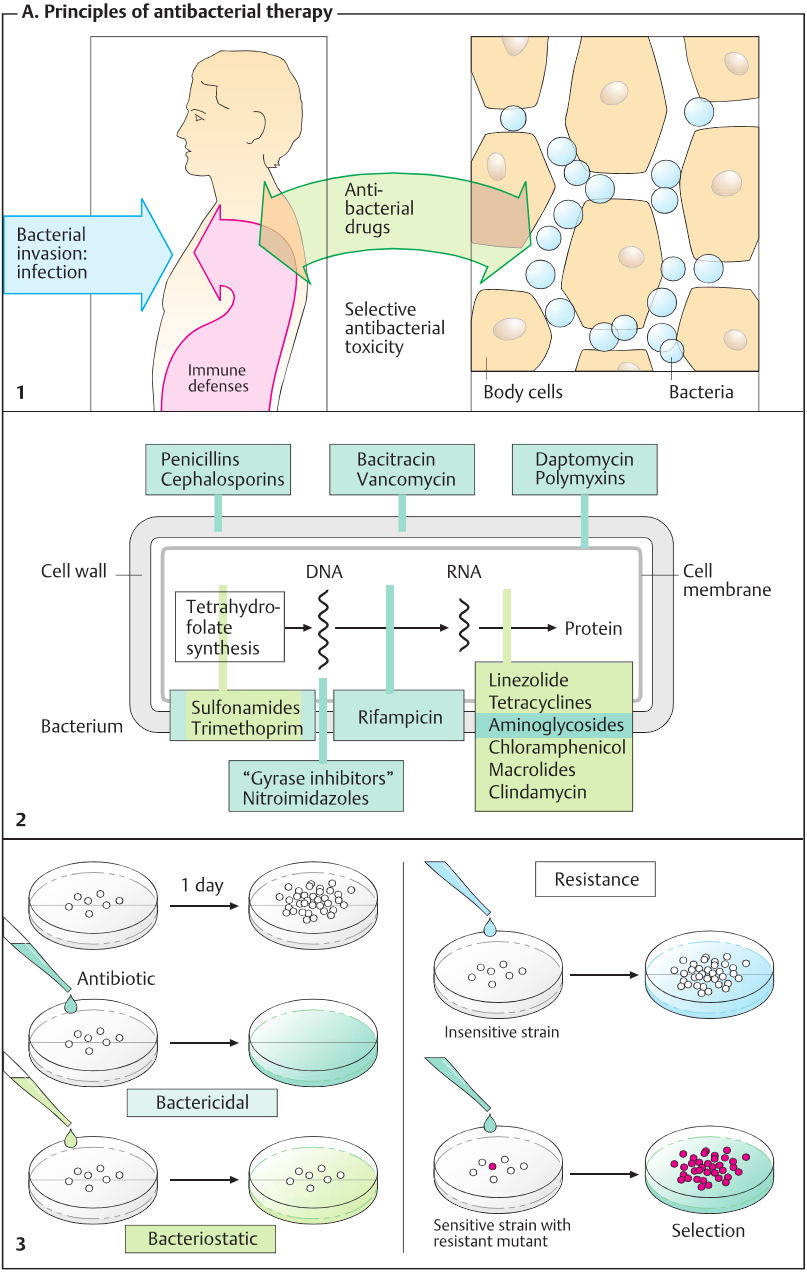

A. Principles of antibacterial therapy
Bacterial invasion: infection
Immune defenses
Anti-bacterial drugs
Selective antibacterial toxicity
Body cells
Bacteria
1
Penicillins Cephalosporins
Bacitracin Vancomycin
Daptomycin Polymyxins
Cell wall
Cell membrane
DNA
RNA
Tetrahydro-folate synthesis
Protein
Sulfonamides Trimethoprim
Rifampicin
Linezolide
Tetracyclines
Aminoglycosides
Chloramphenicol
Macrolides
Clindamycin
Bacterium
"Gyrase inhibitors" Nitroimidazoles
2
1 day
Antibiotic
Bactericidal
Bacteriostatic
Resistance
Insensitive strain
Sensitive strain with resistant mutant
Selection
3

Fig. 30.1

Inhibitors of Cell Wall Synthesis

In most bacteria, a cell wall surrounds the cell like a rigid shell that protects against noxious outside influences and prevents rupture of the plasma membrane from a high internal osmotic pressure. The structural stability of the cell wall is due mainly to the **murein (peptidoglycan) lattice.** This consists of basic building blocks linked together to form a large macromolecule. Each basic unit contains the two linked amino sugars *N*-acetyl-glucosamine and *N*-acetylmuramic acid; the latter bears a peptide chain. The building blocks are synthesized in the bacterium, transported outward through the cell membrane, and assembled as illustrated schematically. The enzyme transpeptidase cross-links the peptide chains of adjacent amino-sugar chains. Bacteria that stain Gram-negative have an additional membrane outside the murein layer. For many antibiotics, this blocks access to Gram-negative bacteria. This membrane consists of a phospholipid double layer containing proteins (including transport proteins that allow antibiotics to pass through) along with lipopolysaccharides.

Inhibitors of cell wall synthesis are suitable antibacterial agents because animal, including human, cells lack a cell wall. These agents exert a **bactericidal** action on growing or multiplying germs. Members of this class include β-lactam antibiotics such as the *penicillins, cephalosporins* and atypical *β-lactams,* as well as *vancomycin* and *bacitracin.*

► **Penicillins** (► **Fig. 30.2A**). The parent substance of this group is **penicillin G (benzylpenicillin**). It is obtained from cultures of mold fungi, originally from *Penicillium notatum.* Penicillin G contains the basic structure common to all penicillins, **6-aminopenicillanic acid** (6-APA; p. 270) comprising a thiazolidine and a 4-membered **β-lactam ring.** 6-APA itself lacks antibacterial activity. Penicillins disrupt cell wall synthesis by inhibiting **transpeptidase** irreversibly. When bacteria are in their growth and replication phase, penicillins are bactericidal; as a result of cell wall defects, the bacteria swell and burst.

Penicillins are generally well tolerated; with penicillin G, the **daily dose** can range from approx. 0.6 g i.m. (= 10^6 international units, 1 Mega IU [MIU]) to 60 g by infusion. The most important **adverse effects** are due to *hypersensitivity* (incidence up to 5%), with manifestations ranging from skin eruptions to anaphylactic shock (in less than 0.05% of patients). Known penicillin allergy is a contraindication for these drugs. *Neurotoxic effects,* mostly convulsions due to GABA antagonism, may occur if the brain is exposed to extremely high concentrations, e.g., after rapid i.v. injection of a large dose or intrathecal injection.

Penicillin G undergoes rapid renal **elimination** mainly in unchanged form (plasma $t_{1/2}$ ~0.5 hours) by means of a secretion system for organic ions.

To extend the dosing interval while ensuring the necessary antibacterial drug levels, penicillins can be given in high dose because of their wide therapeutic safety margin. Depot preparations are available for intramuscular injection (duration of action of procaine penicillin G is 1 day and that of benzathine penicillin G is 7–28 days). Giving probenecid at the same time to inhibit the renal anion transporter delays elimination; this is now obsolete.

Although very well tolerated, **penicillin G** has **disadvantages** (► Fig. 30.2A) that limit its therapeutic usefulness: (1) it is inactivated by gastric acid, which cleaves the β-lactam ring, necessitating parenteral administration. (2) The β-lactam ring can also be opened by bacterial enzymes (β-lactamases); in particular, penicillinase, which can be produced by staphylococcal strains, renders them resistant to penicillin G. (3) The antibacterial spectrum is narrow; although it encompasses many Gram-positive bacteria, Gram-negative cocci, and spirochetes, many Gram-negative pathogens are unaffected.

A. Penicillin G: origin, structure, action

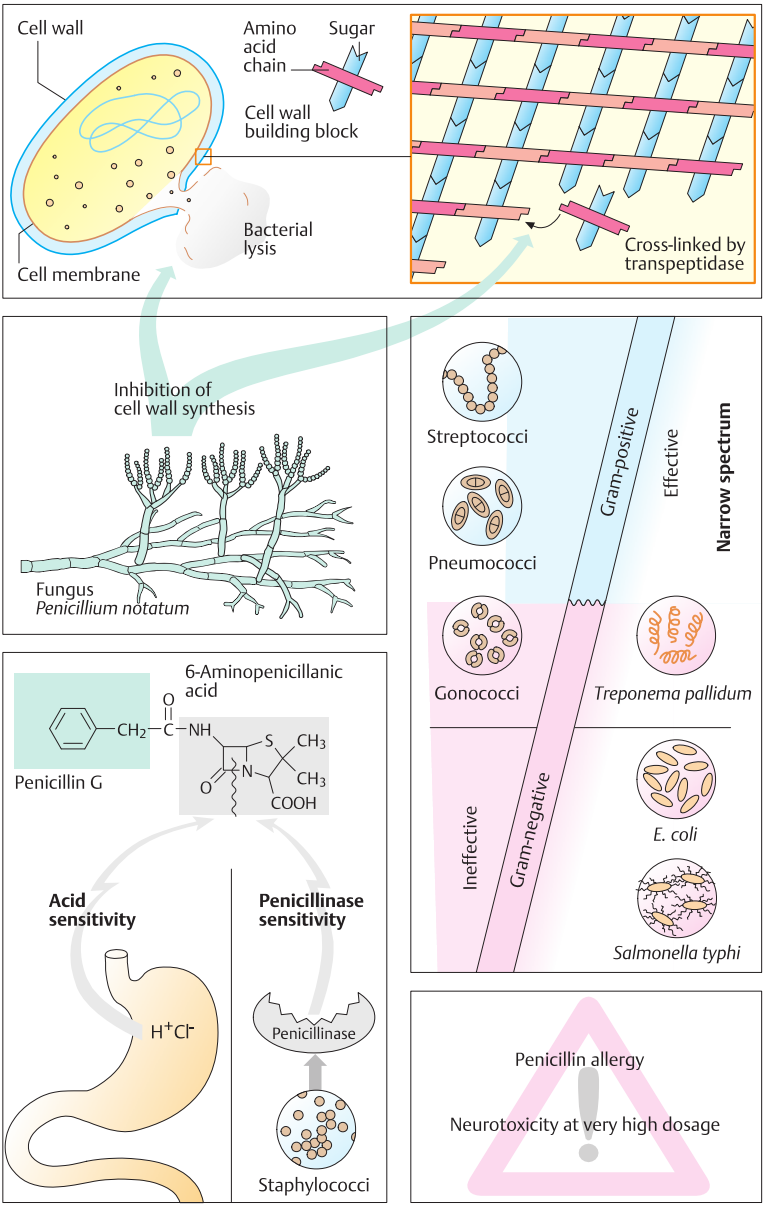


Fig. 30.2

Penicillin derivatives with different substituents on 6-APA possess certain advantages:

1. **Acid resistance** permits oral administration, provided that enteral absorption is possible. Many of the derivatives shown in ▶ Fig. 30.3**A** can be given orally. *Penicillin V* (phenoxymethylpenicillin) exhibits antibacterial properties similar to those of penicillin G.
2. Owing to their **penicillinase resistance**, *isoxazolyl penicillins (oxacillin, dicloxacillin, flucloxacillin)* are suitable for the (oral) treatment of infections caused by penicillinase-producing staphylococci.
3. **Extended activity spectrum:** The aminopenicillin *amoxicillin* is active against many Gram-negative organisms, e.g., colibacteria or *Salmonella typhi*.

Amoxicillin is acid-stable and is absorbed well from the intestine because it uses a dipeptide transporter. *Ampicillin* has a similar spectrum of activity but because it is poorly absorbed (<50%), it therefore causes more extensive damage to the gut microbial flora (side effect: diarrhea), and it should be given only by injection.

Acylaminopenicillins (mezlocillin, piperacillin) show an even broader spectrum against Gram-negative bacteria (including pseudomonad bacteria). These substances are neither acid-stable nor penicillinase-resistant.

Penicillinase-sensitive penicillins become effective against penicillinase producers when they are given together with a β-lactamase inhibitor, which itself has no antibacterial action but irreversibly blocks the enzyme: *clavulanic acid, sulbactam, tazobactam.*

▶ **Cephalosporins (▶ Fig. 30.3A).** These β-lactam antibiotics are also fungal products and have bactericidal activity due to **inhibition of transpeptidase.** Their shared basic structure is 7-aminocephalosporanic acid, as exemplified by *cefalexin* (gray rectangle). Cephalosporins are acid-stable, but many are poorly absorbed. Because they must be given parenterally, most—including those with high activity—are used only in clinical settings. A few, e.g., cefalexin, are suitable for oral use. Cephalosporins are penicillinase-resistant but cephalosporinase-forming organisms do exist. However, some derivatives are also resistant to this β-lactamase. Cephalosporins are broad-spectrum antibacterials. Newer derivatives (e.g., cefotaxime, ceftriaxone, ceftazidime, ceftaroline) are also effective against pathogens resistant to various other antibacterials. Cephalosporins are mostly well tolerated. All can cause allergic reactions, some also renal injury, alcohol intolerance, and bleeding (vitamin K antagonism).

Atypical β-lactams are reserve antibiotics for when penicillins and cephalosporins are ineffective or not tolerated. Following glomerular filtration, the **carbapenem** *imipenem* is inactivated in the lumen of the proximal tubule by a dehydropeptidase located in the brush border. Combining it with the enzyme inhibitor cilastatin protects against this and maintains efficacy as far as the lower urinary tract. *Meropenem* and *doripenem* are not sensitive to this breakdown and have less CNS toxicity.

In the **monobactam** *aztreonam,* only the core structure of the β-lactams is present in the β-lactam ring.

▶ **Other inhibitors of cell wall synthesis.** Bacitracin and vancomycin interfere with the transport of peptidoglycans through the cytoplasmic membrane and are only active against Gram-positive bacteria. **Vancomycin** is a microbial glycopeptide containing unusual amino acids so that it cannot be cleaved in the gastrointestinal tract. It can be used for the (oral) treatment of bowel inflammations occurring as a complication of antibiotic therapy (pseudomembranous enterocolitis caused by *Clostridium difficile).* It is not absorbed. Infections with Gram-positive cocci that are resistant against better tolerated drugs can also be treated with vancomycin given systemically. This entails an increased risk of ototoxicity (hearing loss, tinnitus) or vestibular toxicity (vertigo, ataxia, and nystagmus).

Bacitracin is a polypeptide mixture; it is markedly nephrotoxic and is used only topically.

A. Inhibitors of cell wall synthesis

	Route	β-Lactamase	Spectrum (gram ⊕ / gram ⊖)	Comment
Penicillins				
Penicillin V		Sensitive		Spectrum of action as penicillin G but acid-resistant
Flucloxacillin, an isoxazolyl penicillin		Penicillinase-resistant		Acid-resistant
Amoxicillin, an amino penicillin		Sensitive		Absorption by enteral dipeptide transporter
Ampicillin		Sensitive		Acid-resistant but poor enteral absorption
Piperacillin, an acylamino penicillin		Sensitive		Also effective against problem bacteria such as *Pseudomonas* spp.
Cephalosporins				
Cefalexin		Penicillinase-resistant Cephalosporinase-sensitive		1st generation
Ceftazidime		Resistant		3rd generation also effective against problem bacteria
Carbapenem				
Imipenem		Resistant (carbapenemase-producing bacteria have been described)		Very broad spectrum reserve drug (+ cilastatin)
Monobactam				
Aztreonam		Resistant (but mono bactam-splitting bacteria have been described)		Reserve drug Inhalational use against pseudomonas in mucoviscidosis
Vancomycin				
Glycopeptides (from *Streptomyces* spp.)		Not applicable		Reserve drug: treatment of *Clostridium difficile* bowel infection Methicillin-resistant *Staph. aureus* (MRSA)
Combination: β-lactamase inhibitors				
Clavulanic acid				Sulbactam

Fig. 30.3

Pore Formers and Inhibitors of THF Synthesis

Pore Formers

The bacterial cell membrane structure is quite unsuitable as a target for antibacterial therapy. Substances that increase the permeability of bacterial cell membranes are seldom tolerated by the host.

Daptomycin is a pore former (▶ Fig. 30.4**A**) that attaches to the cell membrane with its lipophilic carbohydrate chain. It has a bactericidal action against Gram-positive bacteria. It can be used as a reserve agent for severe skin and soft tissue infections and is given by infusion. An increase in the blood creatine kinase level can be expected, indicating skeletal muscle damage.

Because of their systemic toxicity, polypeptide antibiotics of the *polymyxin type* (polymyxin B, polymyxin E [Colistin]) are only used locally against Gram-negative bacteria and *tyrothricin* (a peptide mixture of tyrocidins and gramicidins) is used against Gram-positive bacteria.

Inhibitors of Tetrahydrofolate Synthesis

Tetrahydrofolic acid (THF) is a coenzyme in the synthesis of purine bases and thymidine (▶ Fig. 30.4**B**). These are constituents of DNA and RNA and are required for cell growth and replication. Lack of THF leads to inhibition of cell proliferation. Formation of THF from dihydrofolate (DHF) is catalyzed by the enzyme dihydrofolate reductase. DHF is made from folic acid, a vitamin that cannot be synthesized in the body but must be taken up from exogenous sources. Most bacteria do not have a requirement for folate, because they are capable of synthesizing it—more precisely DHF—from precursors. Selective interference with bacterial biosynthesis of THF can be achieved with sulfonamides and trimethoprim.

Sulfonamides such as *sulfamethoxazole* structurally resemble p-aminobenzoic acid (PABA), a precursor in bacterial DHF synthesis. As false substrates, sulfonamides competitively *inhibit* utilization of PABA, and hence *DHF synthesis.* Sulfonamides thus possess *bacteriostatic activity* against a *broad spectrum* of pathogens. Sulfonamides are produced by chemical synthesis. Sulfamethoxazole is well absorbed following oral administration. It is used in combination with trimethoprim. Adverse effects may include allergic reactions, sometimes with severe skin damage (p. 92), and displacement of other plasma protein-bound drugs or bilirubin in neonates (danger of kernicterus, hence contraindication for the last weeks of gestation and in the neonate). Because of the frequent emergence of resistant bacteria, sulfonamides are now rarely used and only a few are still available.

Trimethoprim inhibits bacterial DHF reductase, the human enzyme being significantly less sensitive than the bacterial one (rarely, bone marrow depression). A 2, 4-diaminopyrimidine, trimethoprim has bacteriostatic activity against a broad spectrum of pathogens. It is used mostly as a component of cotrimoxazole.

Cotrimoxazole is a combination of *trimethoprim* and *sulfamethoxazole.* Since THF synthesis is inhibited at two successive steps, the antibacterial effect is better than that of the individual components. Resistant pathogens are infrequent; a bactericidal effect may occur.

Sulfasalazine (▶ Fig. 30.4**C**). Although originally developed as an antirheumatic agent (p. 360), sulfasalazine is used mainly in the treatment of inflammatory bowel disease. Gut bacteria split this compound into the sulfonamide sulfapyridine and *mesalazine (5-aminosalicylic acid).* The latter is probably the anti-inflammatory agent (possibly acting by inhibiting synthesis of interleukin-1, tumor necrosis factor α, leukotrienes), but must be present on the gut mucosa in high concentrations. Coupling to the sulfonamide prevents premature absorption in upper small-bowel segments. The cleaved-off sulfonamide can be absorbed and may produce typical adverse effects (see above). Delayed release (prodrug) formulations of mesalazine without the sulfonamide moiety are available.

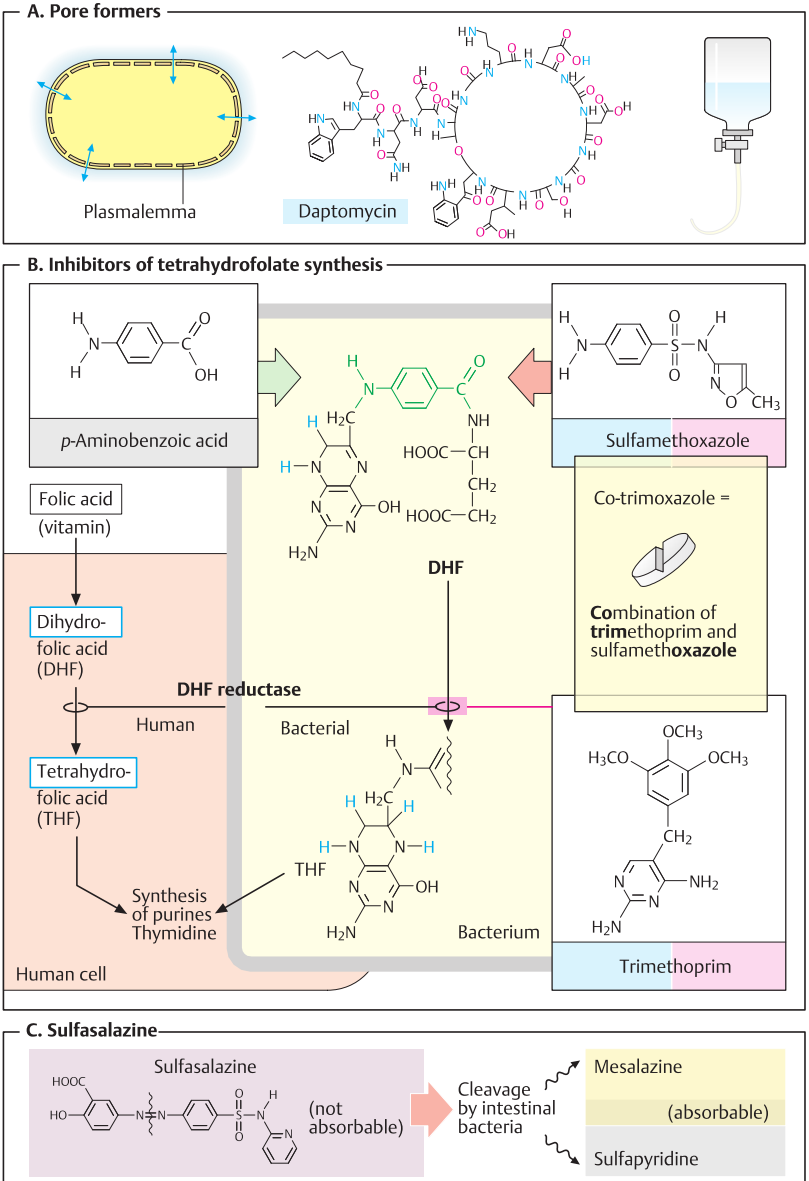

A. Pore formers
Plasmalemma
Daptomycin
B. Inhibitors of tetrahydrofolate synthesis
p-Aminobenzoic acid
Sulfamethoxazole
Folic acid
(vitamin)
Dihydro-
folic acid
(DHF)
DHF reductase
Human
Bacterial
DHF
Co-trimoxazole =
Combination of
trimethoprim and
sulfamethoxazole
Tetrahydro-
folic acid
(THF)
THF
Synthesis
of purines
Thymidine
Human cell
Bacterium
Trimethoprim
C. Sulfasalazine
Sulfasalazine
(not
absorbable)
Cleavage
by intestinal
bacteria
Mesalazine
(absorbable)
Sulfapyridine

Fig. 30.4

Inhibitors of DNA Function

Deoxyribonucleic acid (DNA) serves as a template for the synthesis of nucleic acids. Ribonucleic acid (RNA) executes protein synthesis and thus permits cell growth. Synthesis of new DNA is a prerequisite for cell division. Substances that inhibit reading of genetic information at the DNA template damage the regulatory center of cell metabolism. The substances listed below are useful as antibacterial drugs because they do not affect human cells.

► **Gyrase inhibitors.** The enzyme gyrase (topoisomerase II) permits the orderly accommodation of a ~1000 µm long bacterial chromosome in a bacterial cell of ~1 µm. Within the chromosomal strand, double-stranded DNA has a double helical configuration. The former, in turn, is arranged in loops that are shortened by supercoiling. The gyrase catalyzes this operation, as illustrated, by opening, unwinding, and closing of the DNA double strand such that the full loop need not be rotated.

Derivatives of 4-quinolone-3-carboxylic acid (green portion of ofloxacin formula) are inhibitors of bacterial gyrases. They appear to prevent specifically the resealing of opened strands and thereby act bactericidally. These agents are absorbed after oral ingestion. The fluoroquinolone *norfloxacin* has a broad spectrum but attains effective concentrations only in urine. *Ofloxacin, ciprofloxacin, enoxacin,* and others, also yield systemically effective concentrations and are used for infections of internal organs.

Besides gastrointestinal problems and allergy, adverse effects particularly involve the CNS (confusion, hallucinations, and seizures). Since they can damage epiphyseal chondrocytes and joint cartilages in laboratory animals, gyrase inhibitors should not be used during pregnancy, lactation, and periods of growth. Tendon damage including rupture may occur in elderly or glucocorticoid-treated patients. Several representatives of this group have been withdrawn from the market because of hepatic damage, prolongation of the QT-interval with risk of arrhythmias, derailment of the blood glucose level, and phototoxicity.

► **Nitroimidazole derivatives, such as metronidazole.** These damage DNA by complex formation or strand breakage. This occurs in obligate anaerobic bacteria. Under these conditions, conversion to reactive metabolites that attack DNA takes place (e.g., the hydroxylamine shown). The effect is bactericidal. A similar mechanism is involved in the antiprotozoal action on *Trichomonas vaginalis* (causative agent of vaginitis and urethritis) and *Entamoeba histolytica* (causative agent of large-bowel inflammation, amebic dysentery, and hepatic abscesses). Metronidazole is well absorbed via the enteral route; it is also given i.v. or topically (vaginal pessary). Because metronidazole is considered potentially mutagenic, carcinogenic, and teratogenic in humans, it should not be used for longer than 10 days, if possible, and should be avoided during pregnancy and lactation. *Tinidazole* may be considered equivalent to metronidazole.

► **Rifampicin.** Rifampicin (rifampin) inhibits the bacterial enzyme that catalyzes DNA template-directed RNA transcription, i.e., DNA-dependent RNA polymerase. Rifampicin acts bactericidally against mycobacteria *(Mycobacterium tuberculosis, M. leprae),* as well as many Gram-positive and Gram-negative bacteria. It is well absorbed after oral ingestion. Because resistance may develop with frequent usage, it is virtually restricted to the treatment of tuberculosis and leprosy (p. 280). Rifampicin is contraindicated in the first trimester of gestation and during lactation.

Rifabutin resembles rifampicin but may be effective in infections resistant to rifampicin. The rate of absorption of *rifaximin,* given orally, is < 1%. It is indicated for treatment of traveler's diarrhea and hepatic encephalopathy. *Fidaxomicin,* given orally, is bactericidal against enteral *Clostridium difficile* infections.

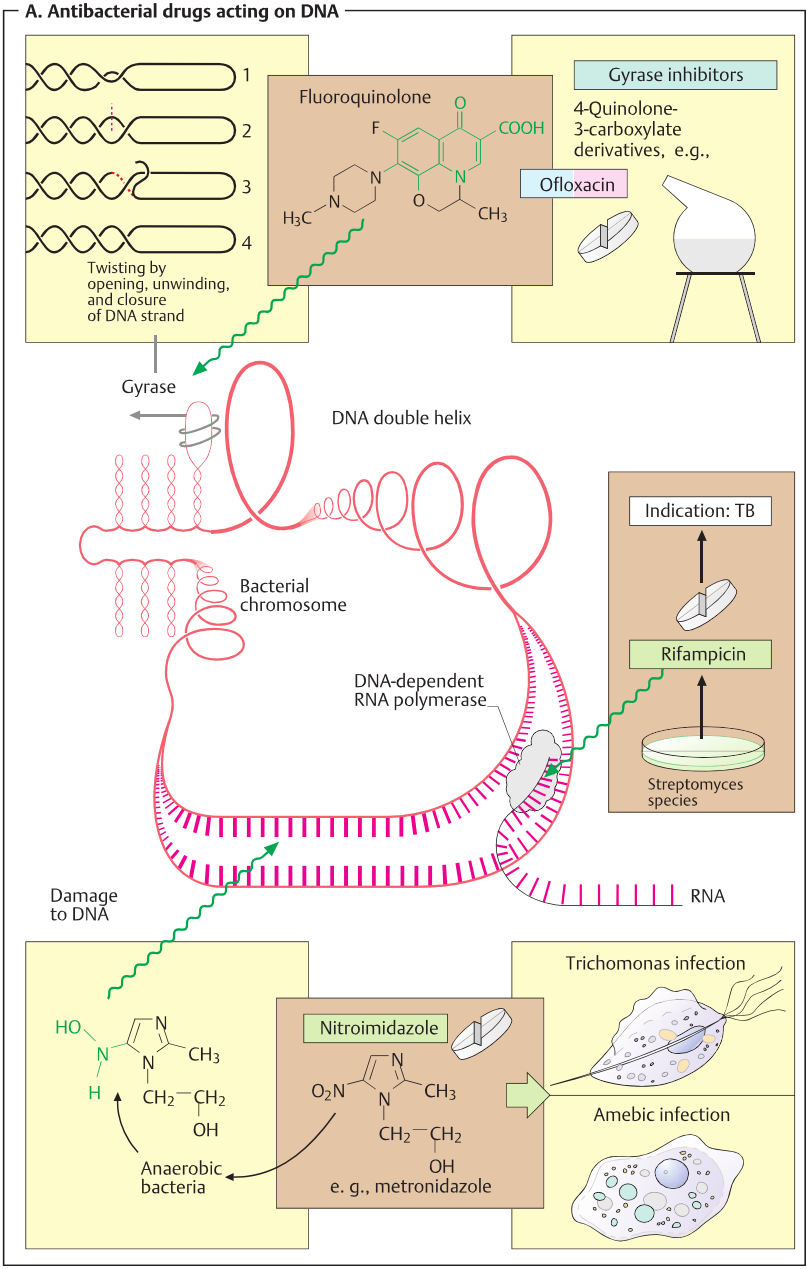

A. Antibacterial drugs acting on DNA
1
2
3
4
Twisting by opening, unwinding, and closure of DNA strand
Fluoroquinolone
F
COOH
O
N
N
O
H_3C
CH_3
Gyrase inhibitors
4-Quinolone-3-carboxylate derivatives, e.g.,
Ofloxacin
Gyrase
DNA double helix
Bacterial chromosome
DNA-dependent RNA polymerase
Indication: TB
Rifampicin
Streptomyces species
RNA
Damage to DNA
HO
N
H
CH_3
CH_2—CH_2
OH
Anaerobic bacteria
Nitroimidazole
O_2N
CH_3
CH_2—CH_2
OH
e. g., metronidazole
Trichomonas infection
Amebic infection

Fig. 30.5

Inhibitors of Protein Synthesis

Protein synthesis means translation into a peptide chain of a genetic message first transcribed into mRNA. Amino acid (AA) assembly occurs at the ribosome. Delivery of amino acids to mRNA involves different transfer RNA molecules (tRNA), each of which binds a specific AA. Each tRNA bears an "anticodon" nucleobase triplet that is complementary to a particular mRNA coding unit *(codon,* consisting of three nucleobases).

Protein synthesis involves the following steps (► Fig. 30.6**A**):

1. Initiation, the first step, involves constructing the protein synthesis apparatus out of mRNA, the small and large ribosome subunit, and the starter tRNA–AA complex. This is followed by the elongation steps.
2. The ribosome "focuses" two codons on mRNA; one (at the left) has bound its tRNA–AA complex, the AA having already been added to the peptide chain; the other (at the right) is ready to receive the next tRNA–AA complex.
3. After the latter attaches, the AAs of the two adjacent complexes are linked by the action of the ribosomal enzyme peptide synthetase (peptidyltransferase). This is a ribozyme, i.e., an enzyme whose catalytic function is provided by ribosomal RNA. Concurrently, AA and tRNA of the left complex disengage.
4. The left tRNA dissociates from mRNA. The ribosome can advance along the mRNA strand and focus on the next codon.
5. Consequently, the right tRNA–AA complex shifts to the left, allowing the next complex to be bound at the right.

These individual steps can be inhibited by antibacterial drugs. Apart from linezolide, which is produced synthetically, all the substances shown in ► Fig. 30.6**A** are derived primarily from *Streptomyces* species. The drug groups are discussed systematically below according to the steps of protein synthesis.

Classification according to their therapeutic importance is different. This is headed by the macrolides and tetracyclines, which are important in ambulant therapy. These are followed by the aminoglycosides, which must be given parenterally and so are reserved for hospital inpatient use, and finally linezolide (a reserve drug) and chloramphenicol, which is now hardly ever used.

1. **Oxazolidinones** such as linezolide are a newly discovered drug group. They inhibit initiation of synthesis of a new peptide strain at the point where ribosome, mRNA, and the "start-tRNA–AA" complex aggregate. Oxazolidinones exert a bacteriostatic effect on Gram-positive bacteria. Since bone marrow depression has been reported, hematological monitoring is necessary. *Linezolide* inhibits monoamine oxidase (MAO-A and MAO-B). Endogenous and ingested biogenic amines may therefore exert an increased effect and increase blood pressure.
2. a) **Tetracyclines** (► Fig. 30.7**A**) inhibit the binding of tRNA–AA complexes. They are bacteriostatic and affect a broad spectrum of pathogens. Tetracyclines are absorbed from the gastrointestinal tract to variable degrees depending on the substance, absorption being nearly complete for *doxycycline* and *minocycline.* Intravenous injection is rarely needed. The most common unwanted effect is *gastrointestinal upset* (nausea, vomiting, diarrhea, etc.) due to (1) a direct mucosal irritant action of these substances and (2) damage to the natural bacterial gut flora (broad-spectrum antibiotics) allowing colonization by pathogenic organisms, including *Candida* fungi. Concurrent ingestion of antacids or milk would, however, be inappropriate because tetracyclines form *insoluble complexes* with *polyvalent cations* (e.g., Ca^{2+}, Mg^{2+}, Al^{3+}, $Fe^{2+/3+}$), resulting in their inactivation; that is, absorbability, antibacterial activity, and local irritant action are abolished. The ability to chelate Ca^{2+} accounts for the propensity of tetracyclines to accumulate in growing teeth and bones. As a result, there occurs an irreversible yellow-brown *discoloration of teeth* and a reversible *inhibition of bone growth.* Because of these adverse effects, tetracycline should not be given after the second month of pregnancy and should not be prescribed to children aged 8 years and under. Other adverse effects are *increased photosensitivity* of the skin and *hepatic damage,* mainly after i.v. administration. **Tigecycline** is a structurally modified derivative of tetracycline (a glycylcycline). It is a reserve drug for severe infections and should also be effective against tetracycline-resistant bacteria.

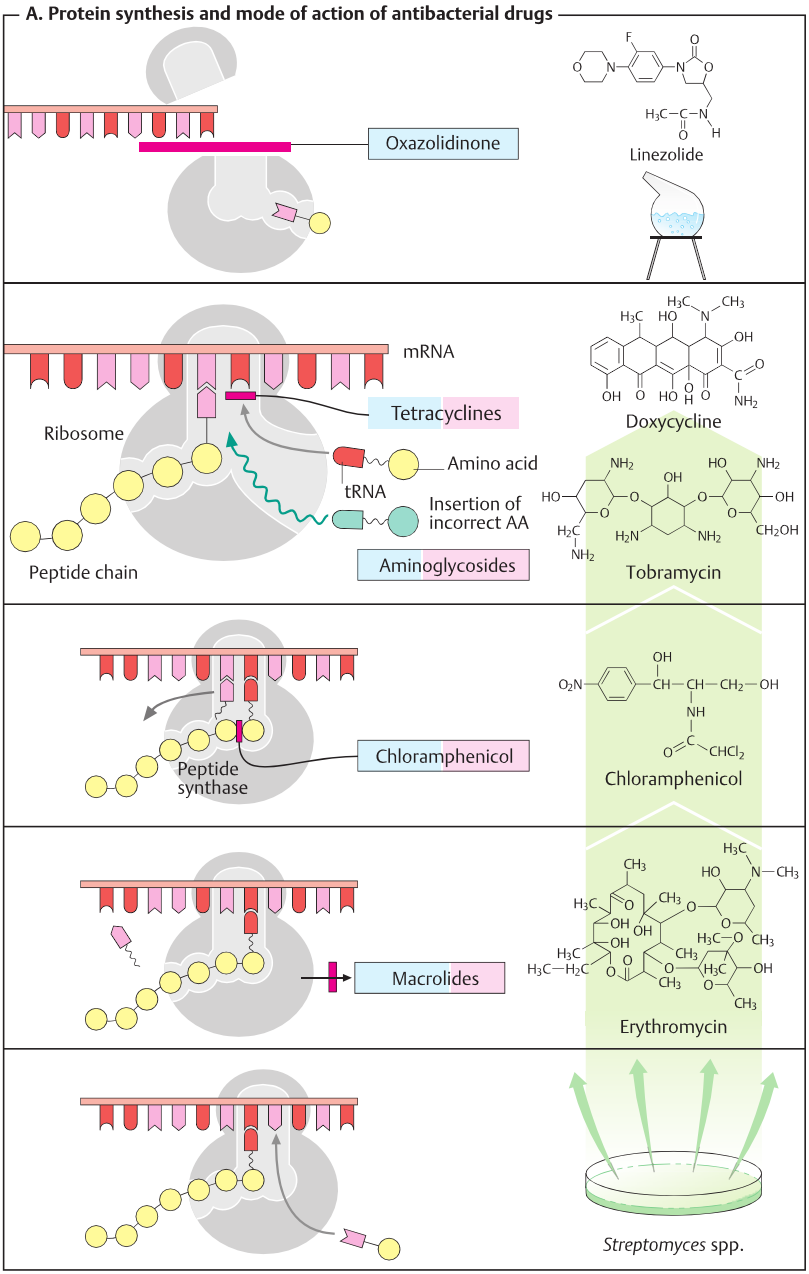

A. Protein synthesis and mode of action of antibacterial drugs
Oxazolidinone
Linezolide
mRNA
Ribosome
Tetracyclines
Amino acid
tRNA
Insertion of incorrect AA
Peptide chain
Aminoglycosides
Doxycycline
Tobramycin
Peptide synthase
Chloramphenicol
Chloramphenicol
Macrolides
Erythromycin
Streptomyces spp.

Fig. 30.6

2. b) **Aminoglycosides** induce the binding of "wrong" tRNA–AA complexes, resulting in synthesis of false proteins. Aminoglycosides are bactericidal. Their activity spectrum encompasses mainly Gram-negative organisms. Streptomycin and kanamycin are used predominantly in the treatment of tuberculosis. Aminoglycosides consist of glycoside-linked amino sugars (cf. gentamicin C_{1a}, a constituent of the gentamicin mixture). They contain numerous hydroxyl groups and amino groups that can bind proteins. Hence, these compounds are highly polar, poorly membrane-permeable and not absorbed enterally. *Neomycin* is only used topically on skin and mucous membranes. Aminoglycosides for systemic treatment of serious infections must be injected (e.g., *gentamicin, tobramycin, paromomycin).* Aminoglycosides gain access to the bacterial interior via bacterial *transport systems.* In the kidney, they enter the cells of the proximal tubules via an uptake system for oligopeptides. Tubular cells are susceptible to damage *(nephrotoxicity,* mostly reversible). In the inner ear, sensory cells of the vestibular apparatus and Corti organ may be injured *(ototoxicity,* sometimes irreversible).
3. **Chloramphenicol** inhibits peptide synthetase. It is bacteriostatic against a broad spectrum of pathogens, is completely absorbed after oral ingestion, and readily crosses diffusion barriers such as the blood–brain barrier. Despite these advantageous properties, use of chloramphenicol is only rarely indicated (e.g., in CNS infections) because of the danger of bone marrow damage.
4. **Macrolides** suppress advancement of the ribosome. Their action is predominantly bacteriostatic and is directed against Gram-positive bacteria. Intracellular germs such as chlamydias and mycoplasmas are also affected. Macrolides are effective orally. The prototype of this group is *erythromycin,* also suitable as a substitute in penicillin allergy or resistance. *Clarithromycin, roxithromycin,* and *azithromycin* are erythromycin derivatives with similar activity; however, their elimination is slower, which permits a reduction in dosage and less frequent administration. Macrolides are usually well tolerated. Gastrointestinal disturbances may occur, possibly because macrolides stimulate the receptor for the endogenous messenger motilin, which stimulates peristalsis. Erythromycin and other macrolides can inhibit cardiac repolarization in the heart, resulting in a risk of cardiac arrhythmias in patients with a pre-existing prolonged QT interval on ECG or who are on concomitant treatment with other drugs that prolong the QT interval. Because of inhibition of CYP isoenzymes such as CYP3A4, there is a risk of drug interactions. Prolonged use can lead to liver damage with cholestasis.

► **Lincosamides.** *Clindamycin* has antibacterial activity similar to erythromycin. It exerts a bacteriostatic effect mainly on Gram-positive aerobic as well as on anaerobic pathogens. Clindamycin is absorbed well after oral ingestion and reaches effective concentrations even in bone, so it is used in the treatment of staphylococcal osteomyelitis.

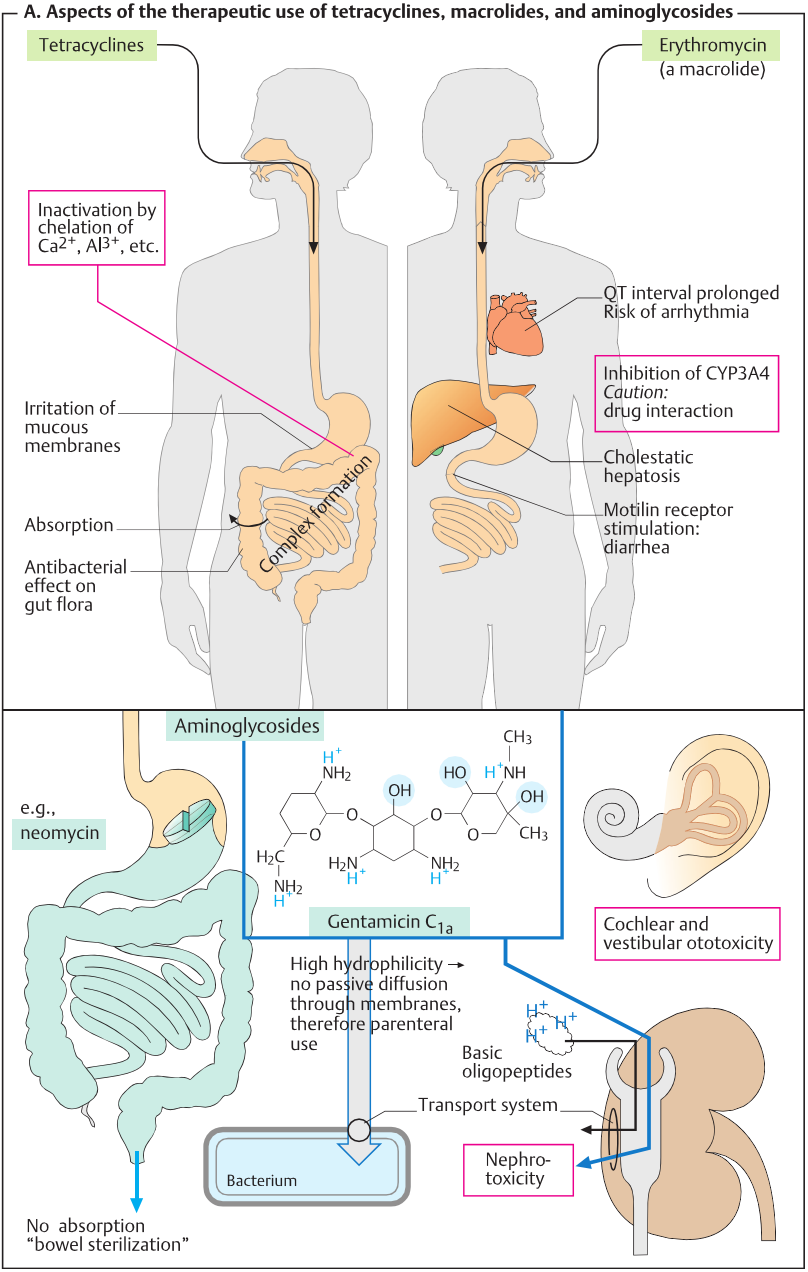

A. Aspects of the therapeutic use of tetracyclines, macrolides, and aminoglycosides
Tetracyclines
Erythromycin
(a macrolide)
Inactivation by chelation of Ca^{2+}, Al^{3+}, etc.
QT interval prolonged
Risk of arrhythmia
Inhibition of CYP3A4
Caution:
drug interaction
Irritation of mucous membranes
Cholestatic hepatosis
Absorption
Complex formation
Motilin receptor stimulation: diarrhea
Antibacterial effect on gut flora
Aminoglycosides
e.g.,
neomycin
Gentamicin C_{1a}
Cochlear and vestibular ototoxicity
High hydrophilicity → no passive diffusion through membranes, therefore parenteral use
Basic oligopeptides
Transport system
Bacterium
Nephro-toxicity
No absorption
"bowel sterilization"

Fig. 30.7

Drugs for Treating Mycobacterial Infections

In the past 100 years, advances in hygiene have led to a drastic decline in **tubercular** diseases in developed countries. Infection with *Mycobacterium tuberculosis* can in most cases be cured by a systematic long-term therapy (6–12 months) with effective chemotherapeutics. Worldwide, however, tuberculosis has remained one of the most threatening diseases. In developing countries, long-term combination therapy is scarcely realizable. Therapeutic success is thwarted by inadequate medical infrastructure, a lack of financial resources, and poor patient compliance. As a result, millions of persons die annually of tuberculosis infections. The insufficient treatment entails an additional bad consequence: more and more mycobacterial strains develop resistance, increasingly to several drugs at the same time (extremely drug-resistant tuberculosis, XDR-TB), and cannot be adequately treated. Patients suffering from immune deficiency are affected more severely by infections with *M. tuberculosis*.

Antituberculosis Drugs

Drugs of choice are isoniazid, rifampicin, and ethambutol, along with streptomycin and pyrazinamide. Combinations of three or four drugs are used in the initial months of treatment.

Isoniazid is bactericidal against growing *M. tuberculosis*. In the bacterium it is converted by a catalase/peroxidase to isonicotinic acid, which accumulates within the cell, where it inhibits synthesis of mycolic acids. These normally form a coat that protects against the host's immune mechanisms. Mycolic acids are linked by the polysaccharide arabinogalactan, which mediates attachment to the murein of the cell wall. Isoniazid is rapidly absorbed after oral administration. In the liver, it is inactivated by acetylation. Notable adverse effects are peripheral neuropathy, optic neuritis preventable by administration of vitamin B_6 (pyridoxine), and liver damage.

Rifampicin. Source, antibacterial activity, and routes of administration are described on p. 274. Although mostly well tolerated, this drug may cause several adverse effects including hepatic damage, hypersensitivity with flu-like symptoms, disconcerting but harmless red/orange discoloration of body fluids, and enzyme induction (failure of oral contraceptives). Concerning rifabutin, see p. 274.

Pyrazinamide likewise inhibits mycolic acid synthesis via an active metabolite. It is given orally. It may impair liver function and cause hyperuricemia by inhibiting renal urate elimination.

Delamanid, another inhibitor of mycolic acid synthesis, is a reserve drug to treat multi-drug-resistant tuberculosis.

Streptomycin must be given i.v. like other aminoglycoside antibiotics (pp. 278–280). It damages the inner ear and the labyrinth. Its nephrotoxicity is comparatively minor.

Ethambutol inhibits the synthesis of arabinogalactan. Ethambutol is given orally. It is generally well tolerated, but may cause dose-dependent reversible disturbances of vision (red/green color blindness, visual field defects).

Bedaquiline inhibits mycobacterial ATP synthase and is bactericidal. It is a reserve drug that can be given orally as part of combined therapy of multi-drug-resistant pulmonary tuberculosis.

Antileprosy Drugs

Rifampicin is frequently given in combination with one or both of the following two agents.

Dapsone is a sulfone that, like sulfonamides, inhibits dihydrofolate synthesis (p. 272). It is bactericidal against susceptible strains of *M. leprae.* Dapsone is given orally. The most frequent adverse effect is methemoglobinemia with accelerated erythrocyte degradation (hemolysis).

Clofazimine is a dye with bactericidal activity against *M. leprae* and anti-inflammatory properties. It is given orally but is incompletely absorbed. Because of its high lipophilicity, it accumulates in adipose and other tissues and leaves the body only rather slowly ($t_{1/2}$ ~70 days). Red-brown skin pigmentation is an unwanted effect, particularly in fair-skinned patients.

A. Drugs used to treat infections with mycobacteria (tuberculosis, leprosy)

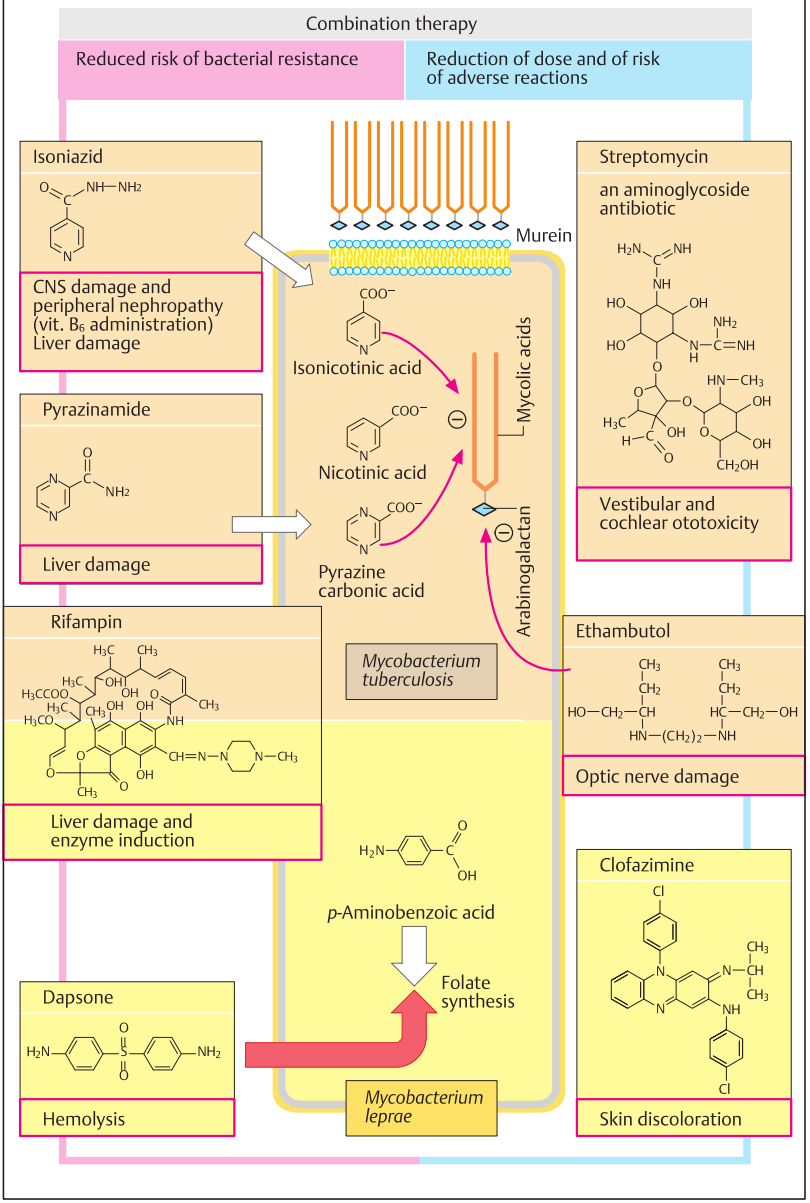


Fig. 30.8

Drugs Used in the Treatment of Fungal Infections

Infections due to fungi are usually confined to the skin or mucous membranes: local or superficial mycosis. However, in immune deficiency states, internal organs may also be affected: systemic or deep mycosis.

Mycoses are most commonly due to *dermatophytes,* which affect the skin, hair, and nails following external infection, and to *Candida albicans,* a yeast organism normally found on body surfaces, which may cause infections of mucous membranes, less frequently of the skin or internal organs when natural defenses are impaired (immunosuppression, or damage of microflora by broad-spectrum antibiotics).

Imidazole derivatives inhibit synthesis of ergosterol, an integral constituent of cytoplasmic membranes of fungal cells and the counterpart to the patient's cholesterol. Fungi stop growing (fungistatic effect) or die (fungicidal effect). The spectrum of affected fungi is very broad. Because they are poorly absorbed and poorly tolerated systemically, most imidazoles are suitable only for topical use *(clotrimazole, econazole, miconazole, sertaconazole). Fluconazole* and *itraconazole* are newer orally effective **triazole** derivatives. Both substances are eliminated slowly (plasma $t_{1/2}$ ~30 hours). Owing to its hydroxyl group, fluconazole is sufficiently water-soluble to allow formulation as an injectable solution. *Voriconazole* is closely related structurally to fluconazole but has a broader spectrum, which includes fungi resistant to fluconazole. The same applies for *posaconazole,* which is related structurally to itraconazole. The **allyl amine** *terbinafine* (oral) and the **morpholine** *amorolfine* (topical) also inhibit ergosterol synthesis, albeit at a different step. Both are used to treat fungal nail infections.

The **polyene antibiotics** amphotericin B and nystatin are of bacterial origin. They insert themselves into fungal cell membranes (probably next to ergosterol molecules) and cause formation of hydrophilic channels. *Amphotericin B* is active against most organisms responsible for systemic mycoses. Because polyene antifungal drugs are nonabsorbable, theymust be given by infusion, which is, however, poorly tolerated (chills, fever, CNS disturbances, impaired renal function, and phlebitis at the infusion site). Applied topically to skin or mucous membranes, amphotericin B is useful in the treatment of candidal infection. Because of the low rate of enteral absorption, oral administration in intestinal candidiasis can be considered a topical treatment. Likewise, *nystatin* is only used topically (e.g., oral cavity, gastrointestinal tract) against candidiasis.

Flucytosine is converted in candidal fungi to 5-fluorouracil by the action of a specific fungal cytosine deaminase. As an antimetabolite, this compound disrupts DNA and RNA synthesis (p. 298), resulting in a fungicidal effect. Given orally, flucytosine is rapidly absorbed. It is often combined with amphotericin B to allow dose reduction of the latter.

Caspofungin is a cyclic polypeptide of the echinocandin type, which inhibit synthesis of the fungal wall by blocking the enzyme β-1,3-glucansynthase. Caspofungin can be used in systemic mycoses due to *Candida* and *Aspergillus* fungi when amphotericin B or itraconazole cannot be employed. It is given by infusion and causes various adverse effects. *Anidulafungin* and *micafungin* act in a similar way.

Griseofulvin (obtained from molds) is a spindle poison. Following oral ingestion, it accumulates in newly formed keratin, where it inhibits growth of dermatophytes. It has to be taken for weeks. It is now virtually obsolete.

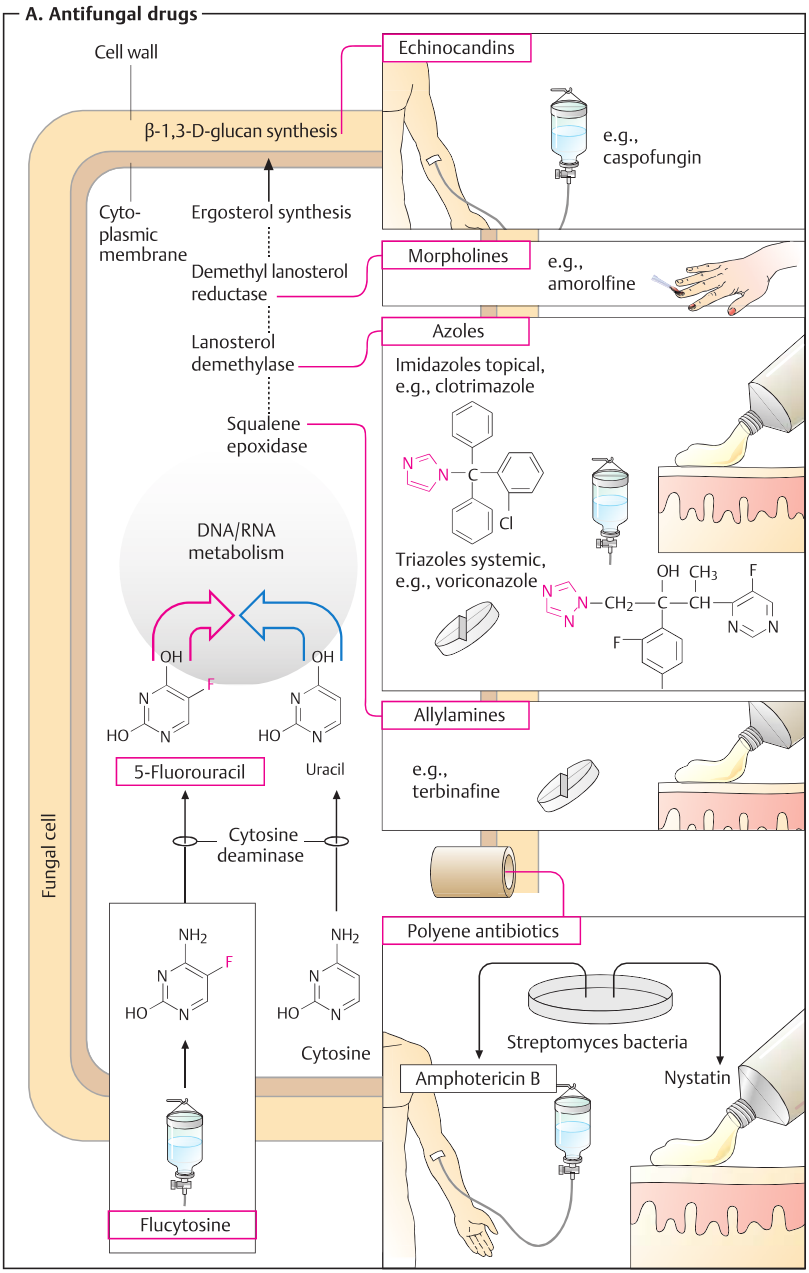

A. Antifungal drugs
Cell wall
β-1,3-D-glucan synthesis
Cyto-
plasmic
membrane
Ergosterol synthesis
Demethyl lanosterol
reductase
Lanosterol
demethylase
Squalene
epoxidase
DNA/RNA
metabolism
5-Fluorouracil
Uracil
Cytosine
deaminase
Cytosine
Flucytosine
Fungal cell
Echinocandins
e.g.,
caspofungin
Morpholines
e.g.,
amorolfine
Azoles
Imidazoles topical,
e.g., clotrimazole
Triazoles systemic,
e.g., voriconazole
Allylamines
e.g.,
terbinafine
Polyene antibiotics
Streptomyces bacteria
Amphotericin B
Nystatin

Fig. 31.1

Pharmacotherapy of Viral Infections

Viruses essentially consist of genetic material (nucleic acids) and a capsular envelope made up of proteins, often with a coat of a phospholipid (PL) bilayer with embedded proteins. They lack a metabolic system and depend on the infected cell for their growth and replication. Targeted therapeutic suppression of viral replication requires selective inhibition of those metabolic processes that specifically serve viral replication in infected cells.

► **Viral replication as exemplified by** ***herpes simplex*** **viruses (► Fig. 32.1A).**

1. The viral particle attaches to the host cell membrane *(adsorption)* via envelope glycoproteins that make contact with specific structures of the cell membrane.
2. The viral coat fuses with the plasmalemma of host cells and the nucleocapsid (nucleic acid plus capsule) enters the cell interior *(penetration).*
3. The capsule opens ("uncoating") near the nuclear pores and viral DNA moves into the cell nucleus. The genetic material of the virus can now direct the cell's metabolic system.
4. a) *Nucleic acid synthesis:* The genetic material (DNA in this instance) is replicated and RNA is produced for the purpose of *protein synthesis.*
   b) The proteins are used as "viral enzymes" catalyzing viral multiplication (e.g., DNA polymerase and thymidine kinase), as capsomers, or as coat components, or are incorporated into the host cell membrane.
5. Individual components are assembled into new virus particles *(maturation).*
6. Release of daughter viruses results in spread of virus inside and outside the organism.

With herpes viruses, replication entails host cell destruction and development of disease symptoms.

► **Antiviral mechanisms (► Fig. 32.1A).** The organism can disrupt viral replication with the aid of cytotoxic T-lymphocytes that recognize and destroy virus-producing cells (presenting viral proteins on their surface) or by means of antibodies that bind to and inactivate extracellular virus particles. Vaccinations are designed to activate **specific immune defenses.**

Interferons (IFN) are glycoproteins that, among other products, are released from virus-infected cells. In neighboring cells, interferon stimulates the production of "antiviral proteins." These inhibit the synthesis of viral proteins by (preferential) destruction of viral DNA or by suppressing its translation. Interferons are not directed against a specific virus, but have a broad spectrum of antiviral action that is, however, species-specific. Thus, interferon for use in humans must be obtained from cells of human origin, such as leukocytes (IFN-α), fibroblasts (IFN-β), or lymphocytes (IFN-γ). Interferons are used in the treatment of certain viral diseases, as well as malignant neoplasms and autoimmune diseases; e.g., IFN-α for the treatment of chronic hepatitis C and hairy cell leukemia; and IFN-β in multiple sclerosis.

Virostatic antimetabolites are "false" DNA building blocks (► Fig. 32.1**B**) or nucleosides. A nucleoside (e.g., thymidine) consists of a nucleobase (e.g., thymine) and the sugar deoxyribose. In antimetabolites, one of the components is defective. In the body, the abnormal nucleosides undergo bioactivation by attachment of three phosphate residues (p. 286).

Trifluridine is incorporated into DNA with deleterious results. This also applies to the synthesis of human DNA. Therefore, trifluridine is suitable only for topical use (in herpes simplex keratitis).

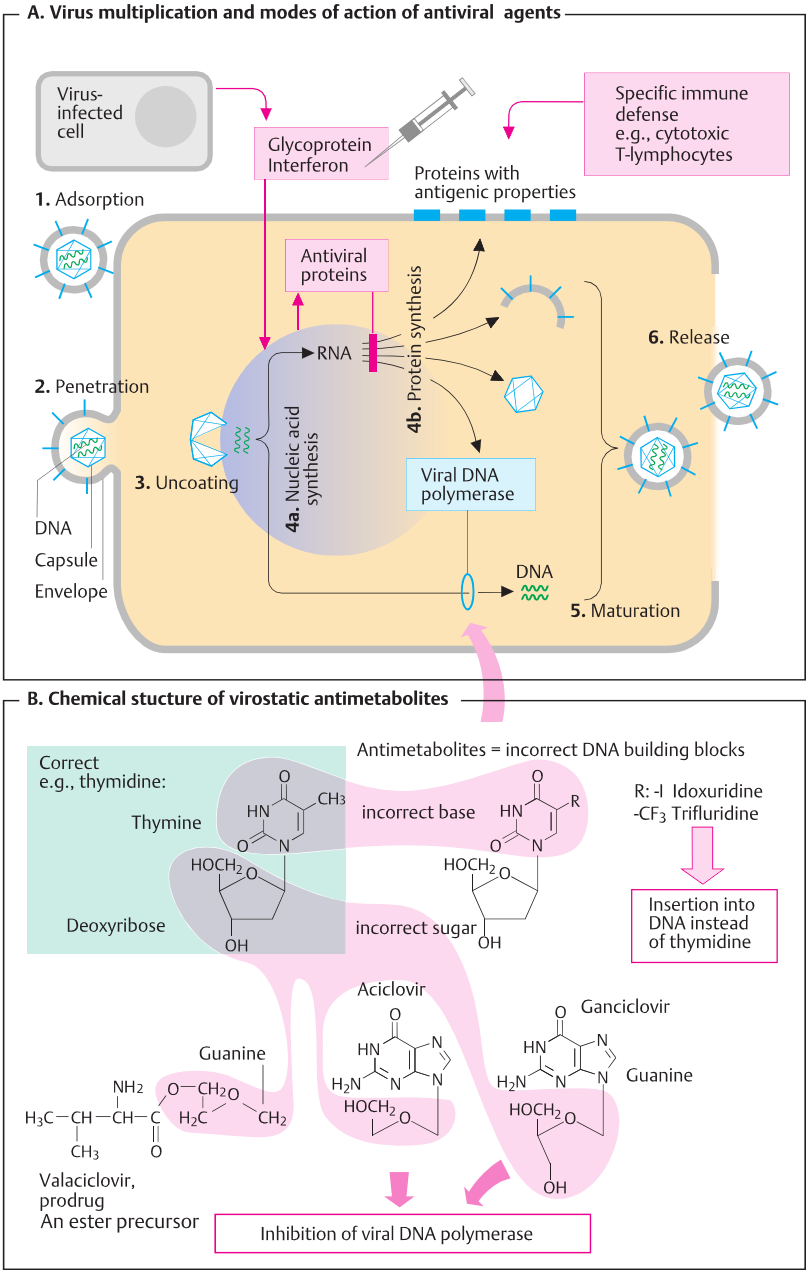

A. Virus multiplication and modes of action of antiviral agents
Virus-infected cell
Glycoprotein Interferon
Specific immune defense e.g., cytotoxic T-lymphocytes
Proteins with antigenic properties
1. Adsorption
Antiviral proteins
RNA
4b. Protein synthesis
6. Release
2. Penetration
3. Uncoating
4a. Nucleic acid synthesis
Viral DNA polymerase
DNA
Capsule
Envelope
DNA
5. Maturation
B. Chemical stucture of virostatic antimetabolites
Correct e.g., thymidine:
Thymine
Deoxyribose
Antimetabolites = incorrect DNA building blocks
incorrect base
incorrect sugar
R: -I Idoxuridine -CF3 Trifluridine
Insertion into DNA instead of thymidine
Aciclovir
Ganciclovir
Guanine
Guanine
Valaciclovir, prodrug An ester precursor
Inhibition of viral DNA polymerase

Fig. 32.1

Among virostatic antimetabolites, **aciclovir** (▶ Fig. 32.2**A**) has high specificity because it undergoes bioactivation only in infected cells, where it preferentially inhibits viral DNA synthesis.

1. A virally coded thymidine kinase (specific to herpes simplex and varicellazoster viruses) performs the initial phosphorylation step; the remaining two phosphate residues are attached by cellular kinases.
2. The polar phosphate residues render aciclovir triphosphate membrane-impermeable and cause it to accumulate in infected cells.
3. Aciclovir triphosphate is a preferred substrate of viral DNA polymerase; it inhibits enzyme activity and, following its incorporation into viral DNA, induces strand breakage because it lacks the 3´-OH group of deoxyribose that is required for the attachment of additional nucleotides. In severe infections with herpes simplex viruses (e.g., encephalitis, generalized infection) and varicella-zoster viruses (e.g., severe herpes zoster), it can be given by i.v. infusion. Aciclovir may also be given orally despite its incomplete (15–30%) enteral absorption. In addition, it has topical uses.

In **valaciclovir,** the hydroxyl group is esterified with the amino acid L-valine (▶ Fig. 32.1**B**). This allows utilization of an enteral dipeptide transporter, leading to an enteral absorption rate almost double that of aciclovir. Subsequent cleavage of the valine residue yields aciclovir.

Ganciclovir (structure in ▶ Fig. 32.1**B**) is used in the treatment of severe infections with **cytomegaloviruses** (also belonging to the herpes group); these do not form thymidine kinase, phosphorylation being initiated by a different viral enzyme. Ganciclovir is less well tolerated and, not infrequently, produces leukopenia and thrombocytopenia. It is infused or administered orally as a valine ester (**valganciclovir**).

Foscarnet represents a diphosphate analogue. It inhibits DNA polymerase by interacting with its binding site for the diphosphate group. *Indication:* topical therapy of herpes simplex infections.

▶ **Drugs used to treat hepatitis viruses** (▶ **Fig. 32.2B**). *Interferon alfa* can be useful against both hepatitis B and hepatitis C viruses (HBV, HCV) during chronic replication. If it is pegylated to peg interferon alfa, drug release from the injection site and renal elimination are slowed, prolonging the duration of action.

Virostatic antimetabolites must be considered separately depending on the pathogen. *Hepatitis B: lamivudine,* originally used only as an anti-HIV agent, is effective against HBV at lower dosage. *Telbivudine* and *entecavir* are also nucleoside derivatives. The phosphonate *adefovir dipivoxil,* which is active against lamivudine-resistant HBV, is an atypical nucleotide. *Hepatitis C:* the molecular mechanism of action of *ribavirin,* in which both the base and the sugar (D-ribose) are altered, is unclear.

Sofosbuvir inhibits *viral RNA polymerase.* A nucleoside analogue monophosphate is released from this inactive precursor, which is rapidly triphosphorylated to the active inhibitor.

Boceprevir and *telaprevir* are inhibitors of *HCV protease.* They suppress cleavage of immature precursors into functioning proteins; production has recently been discontinued (2015).

▶ **Drugs against influenza viruses** (▶ **Fig. 32.2C**). *Amantadine* specifically affects the replication of influenza A (RNA) viruses, the causative agents of true influenza. These viruses are endocytosed into the cell. Release of viral RNA requires protons from the acidic content of endosomes to penetrate into the virus. Amantadine blocks a channel protein in the viral coat that permits influx of protons. Thus, "uncoating" is prevented. The drug is used for prophylaxis and, hence, must be taken before the outbreak of symptoms. It is also an antiparkinsonian drug (p. 334).

Neuraminidase inhibitors prevent the release of influenza A and B viruses. Normally, the viral neuraminidase splits off *N*-acetylneuraminic (sialic) acid residues on the cellular surface coat, thereby enabling newly formed viral particles to be detached from the host cell. *Zanamivir* is given by inhalation; *oseltamivir* is suitable for oral administration because it is an ester prodrug. Uses include treatment and prophylaxis of influenza virus infections.

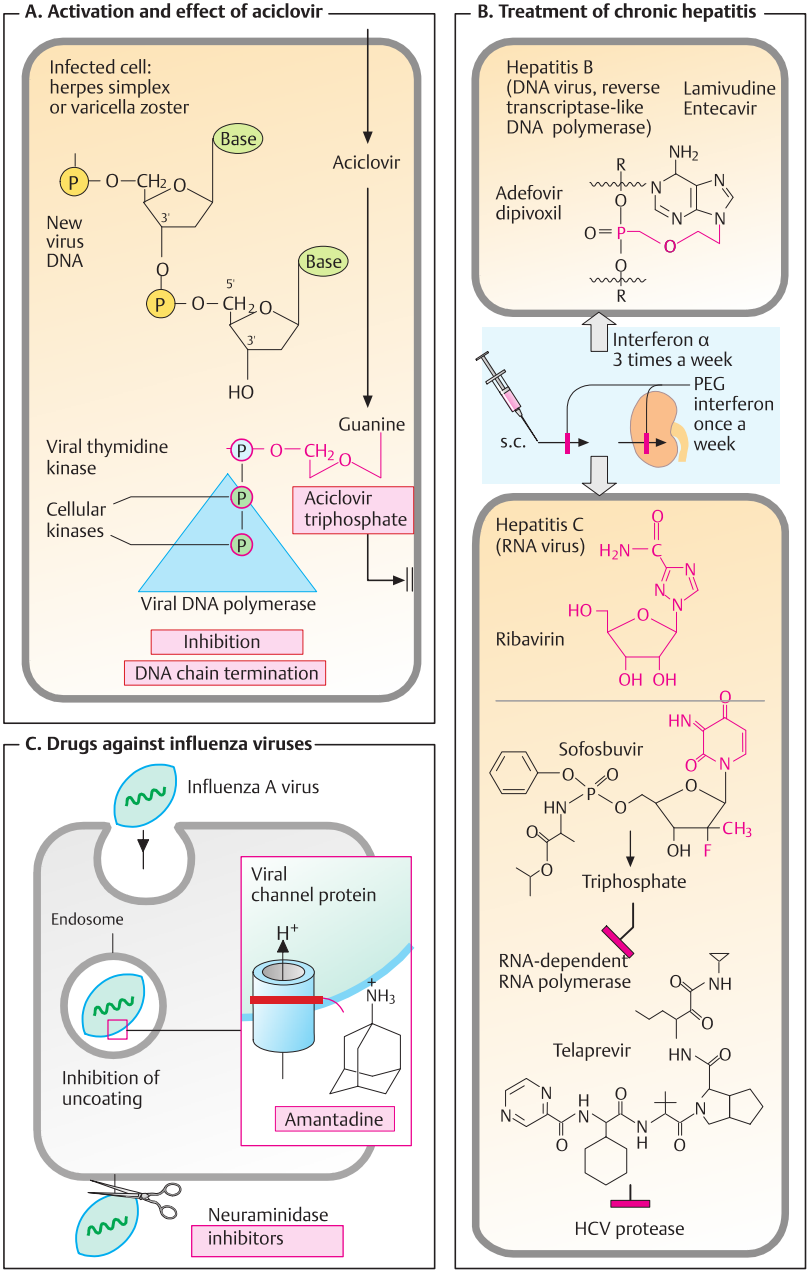

A. Activation and effect of aciclovir
Infected cell:
herpes simplex
or varicella zoster
Aciclovir
New
virus
DNA
Base
Base
HO
Guanine
Viral thymidine
kinase
Cellular
kinases
Aciclovir
triphosphate
Viral DNA polymerase
Inhibition
DNA chain termination
B. Treatment of chronic hepatitis
Hepatitis B
(DNA virus, reverse
transcriptase-like
DNA polymerase)
Lamivudine
Entecavir
Adefovir
dipivoxil
Interferon α
3 times a week
s.c.
PEG
interferon
once a
week
Hepatitis C
(RNA virus)
Ribavirin
Sofosbuvir
Triphosphate
RNA-dependent
RNA polymerase
Telaprevir
HCV protease
C. Drugs against influenza viruses
Influenza A virus
Endosome
Viral
channel protein
Inhibition of
uncoating
Amantadine
Neuraminidase
inhibitors

Fig. 32.2

Drugs for the Treatment of HIV

Replication of the human immunodeficiency virus (HIV), the causative agent of AIDS, is susceptible to targeted interventions because it entails several obligatory steps in virus-specific metabolism (▶ Fig. 32.3**A**). First, the virus docks on monocytes or T-helper lymphocytes by means of a glycoprotein in the viral coat. Both of these cell types carry the CD4 complex (p. 304) but differ in the necessary second chemokine receptor attachment site (CCR5 or CXCR4). After binding, a fusion protein is then extruded from the viral coat, by which fusion of the latter and the cell membrane is initiated. Next, viral RNA is transcribed into DNA, a step catalyzed by viral "reverse transcriptase." Double-stranded DNA is incorporated into the host genome with the help of viral integrase. Under control by viral DNA, viral replication can then be initiated, with synthesis of viral RNA and proteins (including enzymes such as reverse transcriptase and integrase, and structural proteins such as the matrix protein lining the inside of the viral envelope). These proteins are not assembled individually but in the form of *polyproteins.* An N-terminal fatty acid (myristoyl) residue promotes their attachment to the interior face of the plasmalemma. As the virus particle buds off the host cell, it carries with it the affected membrane area as its envelope. During this process, a protease contained within the polyprotein cleaves the latter into individual functionally active proteins.

Inhibitors of Reverse Transcriptase

▶ **Nucleoside Agents.** Representatives of this group include **zidovudine, stavudine, zalcitabine, didanosine,** and **lamivudine.** They are nucleosides containing an abnormal sugar moiety and require bioactivation by phosphorylation (cf. zidovudine in ▶ Fig. 32.3**A**). As triphosphates, they inhibit reverse transcriptase and cause strand breakage following incorporation into viral DNA. The substances are administered orally. In part, they differ in their spectrum of adverse effects (e.g., leukopenia with zidovudine; peripheral neuropathy and pancreatitis with the others) and in the mechanisms responsible for development of resistance. AIDS therapy mostly employs combinations of two members of this group plus either a nonnucleoside inhibitor (see below) or one to two protease inhibitors (see below).

Nonnucleoside Inhibitors

Nevirapine, efavirenz, and **rilpivirine** are active inhibitors of nonnucleoside reverse transcriptase (NNRTI), that is, they do not require phosphorylation. Adverse reactions include rashes and interactions involving cytochrome P450 isozymes (CYP).

HIV Protease Inhibitors

Inhibitors of viral protease prevent cleavage of inactive precursor proteins, and hence viral maturation. They are administered orally.

Saquinavir could be considered an abnormal peptide. Its bioavailability is low. **Ritonavir, indinavir, nelfinavir, amprenavir, tipranavir,** and **darunavir** are other protease inhibitors that in part exhibit markedly higher bioavailability. Biotransformation of these drugs involves CYP enzymes and is therefore subject to interaction with various other drugs metabolized via this route. Prolonged administration may be associated with a peculiar redistribution of adipose tissue and metabolic disturbances (hyperlipidemia, insulin resistance, hyperglycemia).

Reserve Drugs

Maraviroc blocks the chemokine receptor CCR5. It can be given orally when it has been shown that a patient's HI viruses use only this and not an alternative binding site (see above).

Enfuvirtide is a peptide that binds to the viral fusion protein in such a manner as to prevent the necessary change in conformation. It is a reserve drug.

Raltegravir, elvitegravir, and **dolutegravir** inhibit viral integrase, thus blocking integration of virus-coded DNA in the host cell genome.

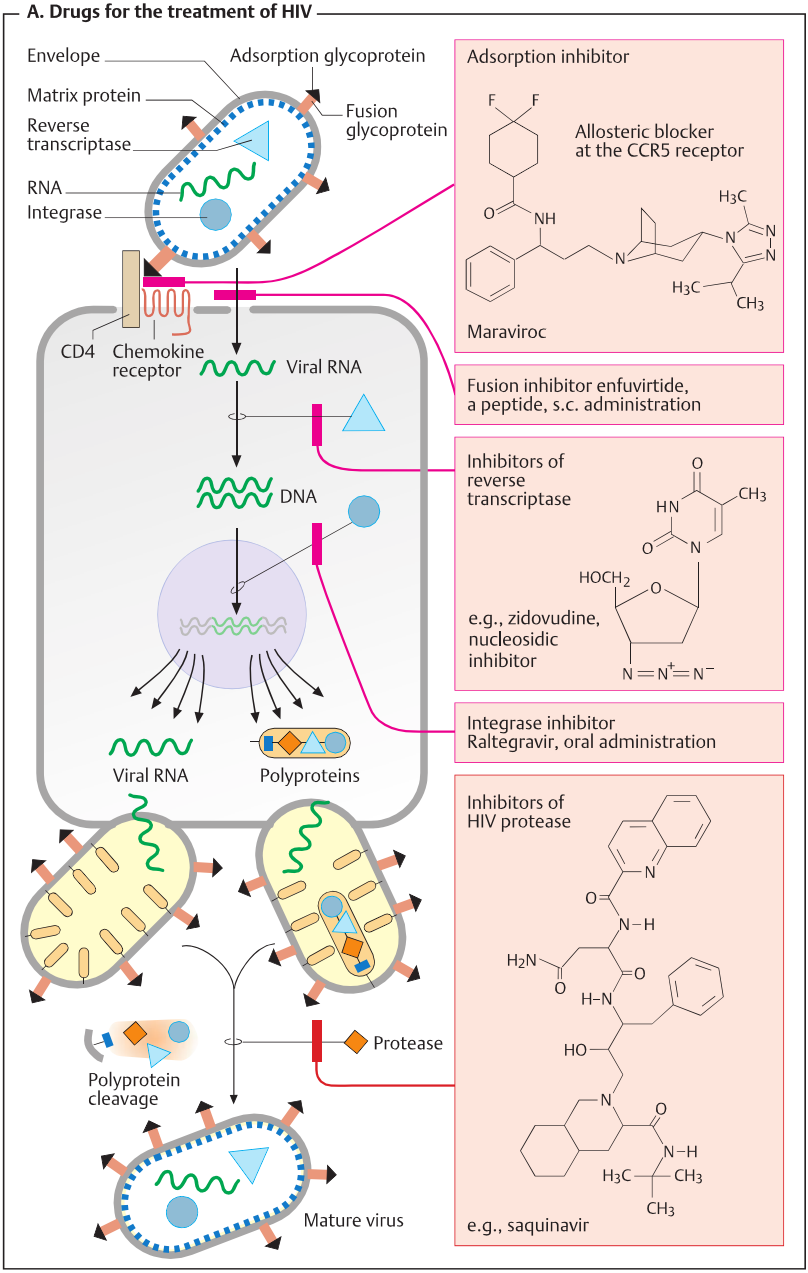

A. Drugs for the treatment of HIV
Envelope
Adsorption glycoprotein
Matrix protein
Fusion glycoprotein
Reverse transcriptase
RNA
Integrase
CD4
Chemokine receptor
Viral RNA
DNA
Viral RNA
Polyproteins
Protease
Polyprotein cleavage
Mature virus
Adsorption inhibitor
Allosteric blocker at the CCR5 receptor
Maraviroc
Fusion inhibitor enfuvirtide, a peptide, s.c. administration
Inhibitors of reverse transcriptase
e.g., zidovudine, nucleosidic inhibitor
Integrase inhibitor Raltegravir, oral administration
Inhibitors of HIV protease
e.g., saquinavir

Fig. 32.3

Drugs for Treating Endoparasitic and Ectoparasitic Infestations

Adverse hygienic conditions favor human infestation with multicellular organisms (referred to here as parasites). Skin and hair are colonization sites for arthropod ectoparasites, such as insects (lice, fleas) and arachnids (mites). Against these, insecticidal and arachnicidal agents, respectively, can be used. Endoparasites invade the intestines or even internal organs and are mostly members of the phyla of flatworms and roundworms. They are combatted with anthelmintics (but cf. filariasis, p. 294).

► **Anthelmintics.** As shown in the table, the newer agents, *praziquantel* and *mebendazole,* are adequate for the treatment of diverse worm diseases. They are generally well tolerated, as are the other agents listed.

► **Insecticides and arachnicides.** Whereas fleas can be effectively dealt with by disinfection of clothes and living quarters, lice and mites require the topical application of therapeutic agents to the infested subject. The following agents act mainly by interfering with the activation or inactivation of neural voltage-gated insect sodium channels.

Chlorphenothane (DDT) kills insects after absorption of a very low amount, e.g., via foot contact with sprayed surfaces (contact insecticide). The cause of death is nervous system damage and seizures. In humans DDT causes acute neurotoxicity only after absorption of very large amounts. DDT is chemically stable and is degraded in the environment and the body at extremely slow rates. As a highly lipophilic substance, it accumulates in fat tissues. Widespread use of DDT in pest control has led to its accumulation in food chains to alarming levels. For this reason its use has now been banned in many countries.

Lindane is the active γ-isomer of hexachlorocyclohexane. It also exerts a neurotoxic action on parasites (as well as humans). Irritation of skin or mucous membranes may occur after topical use. Lindane is active also against intradermal mites (*Sarcoptes scabiei,* causative agent of scabies), besides lice and fleas. Lindane is degraded more readily than DDT.

Pyrethroids (derived from constituents of chrysanthemums) offer an alternative topical therapy for louse and mite infestations; these are *allethrin* and *bioallethrin.* In order to prevent the parasites from rapidly metabolizing the pyrethroids, the topical preparation also contains the CYP inhibitor piperonyl butoxide. *Benzyl benzoate* (25% emulsion) is also effective against scabies.

Table 33.1 Therapy of worm infestations

Worms (helminths)	Anthelmintic drug of choice
Flatworms (platyhelminths)	
• Tape worms (cestodes) • Flukes (trematodes), e.g., *Schistosoma* species (bilharziasis)	• Praziquantel • Praziquantel
Roundworms (nematodes), e.g.,	
• Pinworm *(Enterobius vermicularis, previously known as Oxyuris vermicularis)* • Roundworm *(Ascaris lumbricoides)* • *Trichinella spiralis*	• Mebendazole • Mebendazole • Mebendazole

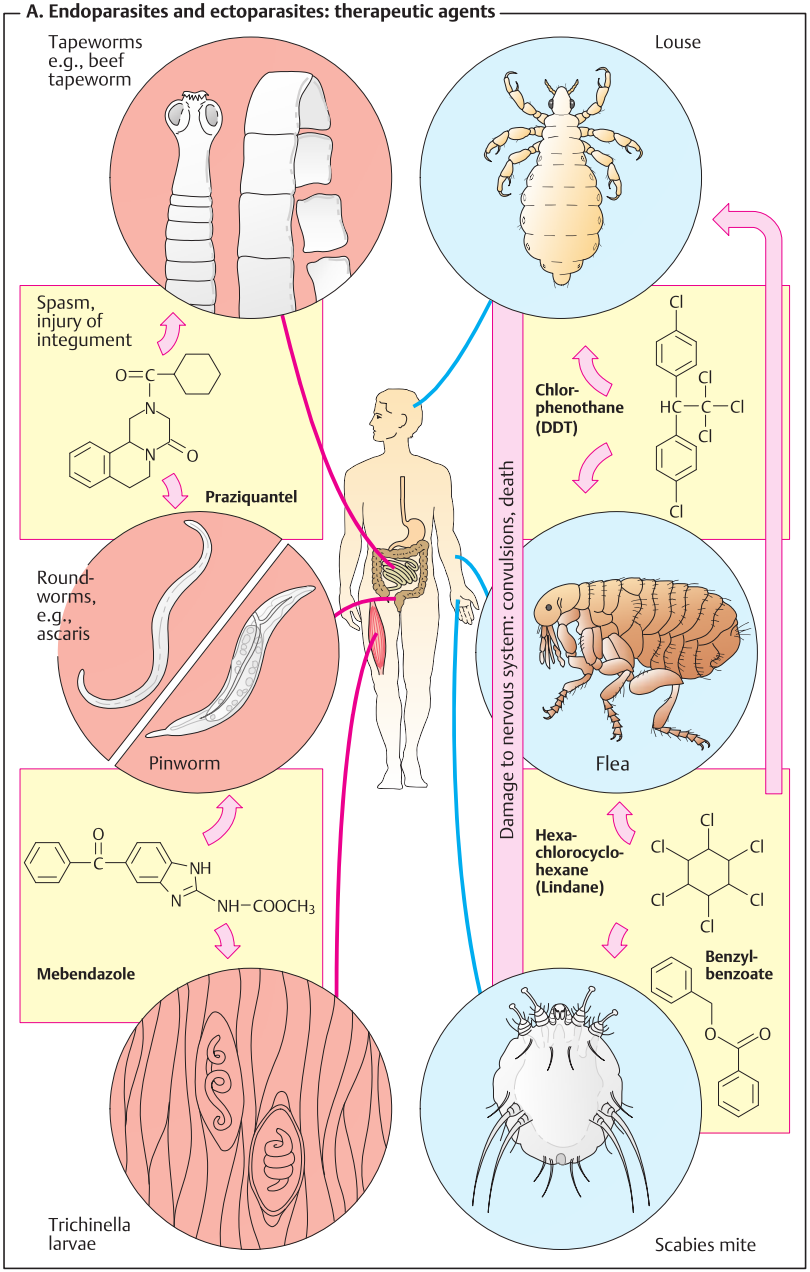

A. Endoparasites and ectoparasites: therapeutic agents
Tapeworms e.g., beef tapeworm
Louse
Spasm, injury of integument
Praziquantel
Chlor-phenothane (DDT)
Damage to nervous system: convulsions, death
Round-worms, e.g., ascaris
Pinworm
Flea
Hexa-chlorocyclo-hexane (Lindane)
Benzyl-benzoate
Mebendazole
Trichinella larvae
Scabies mite

Fig. 33.1

Antimalarial Drugs

The causative agents of malaria are plasmodia, unicellular organisms (order Hemosporidia, class Protozoa). The infective form, the sporozoite, is inoculated into skin capillaries when infected female *Anopheles* mosquitoes (▶ Fig. 34.1**A**) suck blood from humans. Sporozoites invade liver parenchymal cells, where they develop into primary tissue schizonts. These give rise to numerous merozoites that enter the blood. The preerythrocytic stage is asymptomatic. In blood, the parasite enters erythrocytes (erythrocytic stage), where it again multiplies by schizogony, resulting in more merozoites. Rupture of the infected erythrocytes releases the merozoites and pyrogens. A fever attack ensues and more erythrocytes are infected. The generation period for the next crop of merozoites determines the interval between fever attacks. With *Plasmodium vivax* and *P. ovale,* there can be a parallel multiplication in the liver (paraerythrocytic stage). Moreover, some sporozoites may become dormant in the liver as "hypnozoites" before entering schizogony.

Different **antimalarials** selectively kill the parasite's different developmental forms. The "classic" *quinine* and *chloroquine* accumulate in the acidic vacuoles of blood schizonts and inhibit polymerization of heme released from digested hemoglobin, free heme being toxic for schizonts. Mefloquine and *lumefantrine* appear to have a similar mechanism of action. Piperaquine is structurally similar to chloroquine but the resistance pattern differs. *Artemesinin derivatives*, e.g., artemether, also inhibit heme polymerization. They originate from the East Asian plant Qinghaosu *(Artemisia* sp.). Its effect appears to involve a reaction between heme iron and the epoxide group with formation of active metabolites. *Atoquavone* suppresses synthesis of pyrimidine bases, probably by interfering with mitochondrial electron transport. *Proguanil* and cycloguanil, its active form, inhibit protozoal dihydrofolate reductase (p. 272) and thus synthesis of purines and thymidine. The mechanism of action of primaquine is unclear.

Antimalarial drug choice takes tolerability and plasmodial resistance into account.

Plasmodium falciparum, responsible for the most dangerous form of malaria, is particularly prone to develop **drug resistance.** The prevalence of resistant strains rises with increasing frequency of drug use.

▶ **Malaria prophylaxis. Protection from mosquito bites** by skin-covering clothes, repellents, mosquito nets, and insecticides is important. **Pharmacological prophylaxis** can employ agents against blood schizonts: *atovaquone plus proguanil* or *mefloquine* for periods longer than 1 month (elimination half-life 2–3 weeks). It should be noted, however, that mefloquine can cause severe psychiatric disorders. The antibiotic *doxycycline* is also effective, though not approved for this indication. Other possible regimens are *chloroquine* in regions without resistance to this drug and *primaquine* for tertiary malaria infection. *Primaquine* would be effective against primary tissue schizonts of all plasmodial species; however, it is not used for long-term prophylaxis because of unsatisfactory tolerability and the risk of plasmodial resistance.

These drugs do not prevent the (symptom-free) hepatic infection but only the disease-causing infection of erythrocytes ("suppression therapy"). On a person's return from an endemic malaria region, a two-week course of primaquine is adequate for eradication of the late hepatic stages (*P. vivax* and *P. ovale).*

▶ **Malaria therapy.** Different regimens can be used, depending on circumstances (see World Health Organization Guideline, 2015):

- *Artemether + lumefantrine*
- *Atovaquone + proguanil*
- *Piperaquine + dihydroartemesinin*
- *Chloroquine*
- *Mefloquine.*

A. Malaria: stages of the plasmodial life cycle in the human: therapeutic options

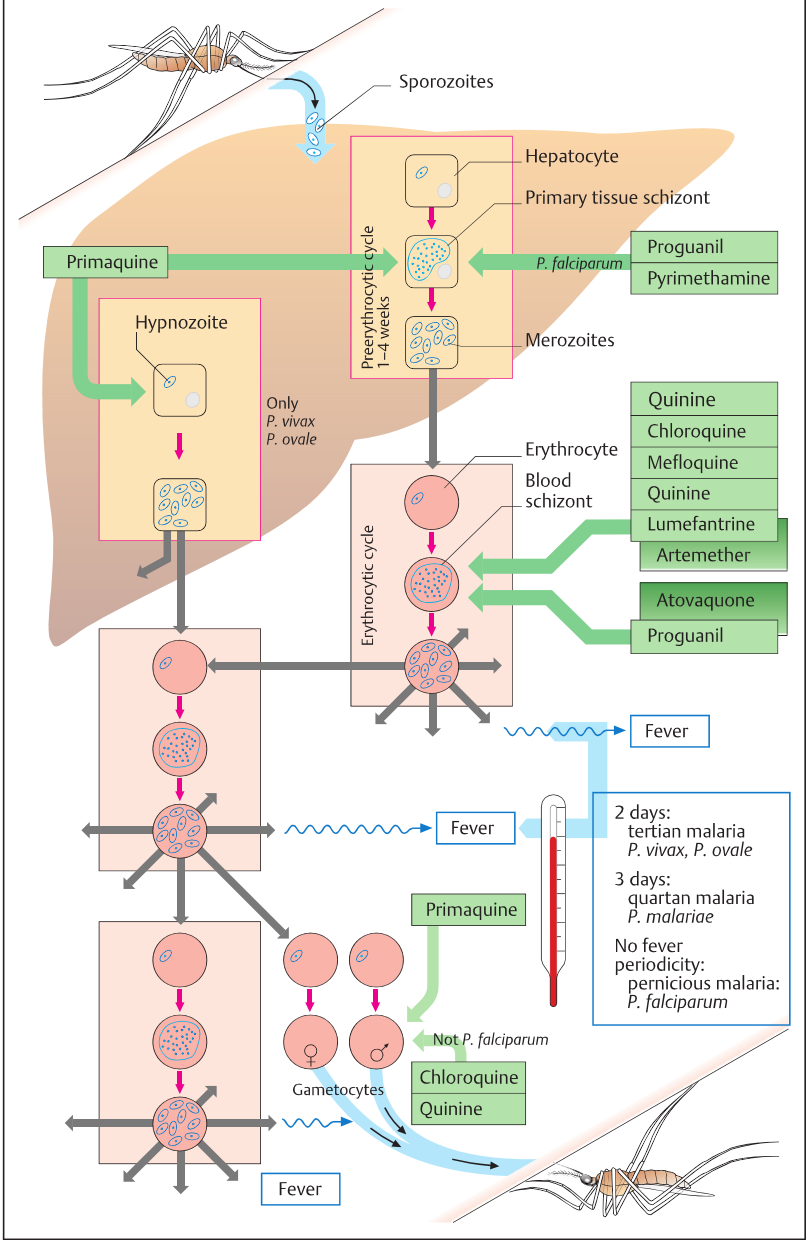


Fig. 34.1

Other Tropical Diseases

In addition to malaria, other tropical diseases and their treatment will be considered for the following reasons. (1) Owing to the tremendous growth in global travel, inhabitants of temperate climatic zones have become exposed to the hazard of infection with tropical disease pathogens. (2) The spread of some tropical diseases is of unimaginable dimensions, with human victims numbering in the millions.

a) **Amebiasis.** The causative agent, *Entamoeba histolytica,* lives and multiplies in the colon (symptom: diarrhea), its cyst form residing also in the liver among other sites. In tropical regions, up to half the population can be infested, transmission occurring by the fecal-oral route. The most effective **treatment** against both intestinal infestation and systemic disease is administration of metronidazole. If monotherapy fails, combination therapy with chloroquine, emetine, or tetracyclines may be indicated.

b) **Leishmaniasis.** The causative agents are flagellated protozoa that are transmitted by sand flies to humans. The parasites are taken up into phagocytes, where they remain in phagolysosomes and multiply until the cell dies and the parasites can infect new cells. **Symptoms:** A visceral form, known as *kala-azar,* and cutaneous or mucocutaneous forms exist (▶ Fig. 34.2**A**). An estimated 12 million humans are affected. **Therapy** is difficult; pentavalent antimonial compounds, such as stibogluconate, must be given for extended periods. Adverse effects are pronounced.

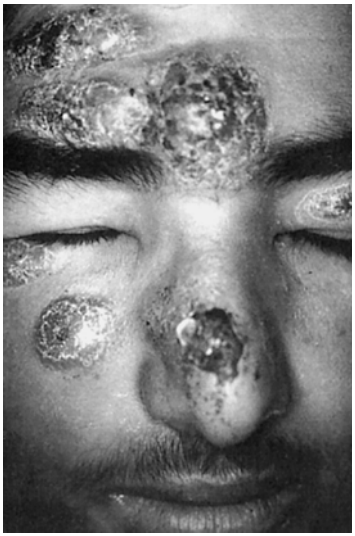
c) **Trypanosomiasis.** The pathogens, *Trypanosoma brucei* (sleeping sickness) and *T. cruzi* (Chagas disease), are flagellated protozoa. ***T. brucei*** (▶ Fig. 34.2**C**) is transmitted by the tsetse fly, distributed in West and East Africa. An initial stage (swelling of lymph nodes, malaise, hepatosplenomegaly, among others) is followed by invasion of the CNS with lethargy, extrapyramidal motor disturbances, Parkinson-like signs, coma, and death. **Therapy:** long-term suramin i.v. (not available in Germany) or pentamidine (less effective); arsenicals (e.g., melarsoprol, highly toxic), when the CNS is involved. ***T. cruzi*** is confined to Central and South America and transmitted by blood-sucking reduviid bugs. These parasites preferentially infiltrate the cardiac musculature, where they cause damage to muscle fibers and the specialized conducting tissue. Death results from cardiac failure. **Therapy:** unsatisfactory.

d) **Schistosomiasis (bilharziasis).** The causative organisms are trematodes with a complex life cycle that need (aquatic) snails as intermediate hosts. Free-swimming larval cercariae penetrate the intact skin of humans. The adult worms *(Schistosoma mansoni,* ▶ Fig. 34.2**D**) live in the venous vasculature. **Occurrence:** tropical countries rich in aquatic habitats. About 200 million humans are afflicted. **Therapy:** praziquantel, 10–40 mg/kg, single dose, is highly effective with minimal adverse effects. Substances released from decaying worms may cause problems.

e) **Filariasis.** In its microform, *Wuchereria bancrofti* is transmitted by mosquitoes; the adult parasites live in the lymph system and cause inflammation and blockage of lymph drainage leading to elephantiasis in extreme cases (▶ Fig. 34.2**B**). **Therapy:** diethylcarbamazepine for several weeks; adverse reactions are chiefly due to products from disintegrating worms.

f) **Onchocerciasis ("River Blindness").** The causative organism is *Onchocerca volvulus,* a filaria transmitted by black flies (genus *Simulium).* The adult parasites (several centimeters long) form tangles and proliferating nodules (onchocercomas) in the skin and have a particular propensity for invading the eyeball, resulting in blindness. About 20 million people inhabiting banks of fast-flowing rivers are afflicted with river blindness. **Therapy:** ivermectin (0.15 mg/kg, single dose); adverse reactions are in part caused by disintegrating worms.

A. Cutaneous leishmaniasis
Causative agent: *Leishmania major*



B. Elephantiasis
Causative agent: *Wuchereria bancrofti*

C. *Trypanosoma brucei*
Causative agent of sleeping sickness

D. *Schistosoma mansoni*
Causative agent of bilharziasis

Fig. 34.2

Chemotherapy of Malignant Tumors

A tumor (neoplasm) consists of cells that proliferate independently of the body's inherent "building plan." A malignant tumor (cancer) is present when the tumor tissue destructively invades healthy surrounding tissue or when dislodged tumor cells form secondary tumors (metastases) in other organs. A cure requires the elimination of all malignant cells (curative therapy). When this is not possible, attempts can be made to slow tumor growth and thereby prolong the patient's life or improve quality of life (palliative therapy). Chemotherapy is faced with the problem that the malignant cells are endogenous and almost lacking in specific metabolic properties.

Cytostatics (▶ Fig. 35.1**A**) are cytotoxic substances that particularly affect proliferating or dividing (mitotic) cells. Rapidly dividing malignant cells are preferentially injured. Damage to mitotic processes not only retards tumor growth but also may initiate *apoptosis* (programmed cell death). Tissues with a low mitosis rate are largely unaffected; likewise, most healthy tissues. This, however, also applies to malignant tumors consisting of slowly dividing differentiated cells.

Tissues that have a physiologically high mitosis rate are bound to be affected by cytostatic therapy. Thus, **typical adverse effects** occur. *Loss of hair* results from injury to hair follicles; *gastrointestinal disturbances,* such as diarrhea, from inadequate replacement of enterocytes whose lifespan is limited to a few days; *nausea and vomiting* from stimulation of area postrema chemoreceptors (p. 342); and *lowered resistance to infection* from weakening of the immune system (p. 304). In addition, cytostatics cause *bone marrow depression.* Resupply of blood cells depends on the mitotic activity of bone marrow stem and daughter cells. When myeloid proliferation is arrested, the short-lived granulocytes are the first to be affected (neutropenia), then blood platelets (thrombocytopenia) and, finally, the more long-lived erythrocytes (anemia). *Infertility* is caused by suppression of spermatogenesis or follicle maturation. Most cytostatics disrupt DNA metabolism. This entails the risk of a potential genomic alteration in healthy cells *(mutagenic* effect). Conceivably, the latter accounts for the occurrence of leukemias several years after cytostatic therapy *(carcinogenic* effect). Furthermore, congenital malformations are to be expected when cytostatics must be used during pregnancy *(teratogenic* effect).

Cytostatics possess different **mechanisms of action.**

▶ **Damage to the mitotic spindle** (▶ **Fig. 35.1B**). The contractile proteins of the spindle apparatus must draw apart the replicated chromosomes before the cell can divide. This process is prevented by the so-called *spindle poisons* (see also colchicine, p. 18) that arrest mitosis at metaphase by disrupting the assembly into spindle threads of microtubules. These consist of the proteins α- and β-tubulin. Surplus tubules are broken down, enabling the tubulin subunits to be recycled.

The vinca alkaloids, *vincristine* and *vinblastine* (from the periwinkle plant *Vinca rosea),* inhibit the polymerization of tubulin subunits into microtubules. Damage to the nervous system is a predicted adverse effect arising from injury to microtubule-operated axonal transport mechanisms.

Paclitaxel, from the bark of the Pacific yew *(Taxus brevifolia),* inhibits disassembly of microtubules and induces formation of atypical ones, and thus impedes the reassemblage of tubulins into properly functioning microtubules. *Docetaxel* is a semisynthetic derivative.

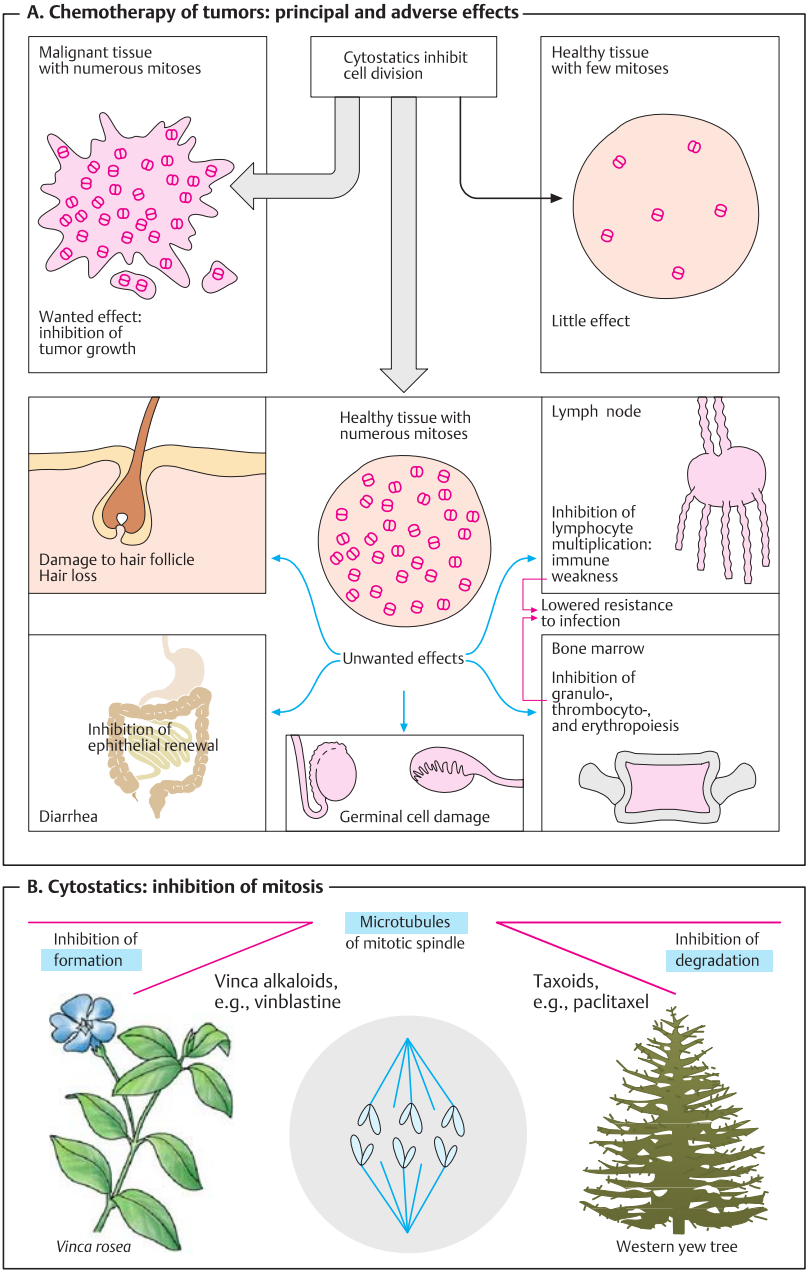

A. Chemotherapy of tumors: principal and adverse effects
Malignant tissue with numerous mitoses
Wanted effect: inhibition of tumor growth
Cytostatics inhibit cell division
Healthy tissue with few mitoses
Little effect
Damage to hair follicle
Hair loss
Healthy tissue with numerous mitoses
Unwanted effects
Lymph node
Inhibition of lymphocyte multiplication: immune weakness
Lowered resistance to infection
Bone marrow
Inhibition of granulo-, thrombocyto-, and erythropoiesis
Inhibition of ephithelial renewal
Diarrhea
Germinal cell damage
B. Cytostatics: inhibition of mitosis
Inhibition of formation
Vinca alkaloids, e.g., vinblastine
Microtubules of mitotic spindle
Inhibition of degradation
Taxoids, e.g., paclitaxel
Vinca rosea
Western yew tree

Fig. 35.1

► **Inhibition of DNA and RNA synthesis** (► **Fig. 35.2A**). Mitosis is preceded by replication of chromosomes (DNA synthesis) and increased protein synthesis (RNA synthesis). Existing DNA (gray) serves as a template for the synthesis of new (blue) DNA or RNA. Denovo synthesis may be inhibited by the following mechanisms.

► **Damage to the template** (► **Fig. 35.21**). **Alkylating cytostatics** are reactive compounds that transfer alkyl residues into a covalent bond with DNA. For instance, *mechlorethamine (nitrogen mustard)* is able to cross-link double-stranded DNA on giving off its chlorine atoms. Correct reading of genetic information is thereby rendered impossible. Other alkylating agents are *chlorambucil, melphalan, cyclophosphamide, ifosfamide, lomustine, thiotepa, mitomycin, procarbazine, dacarbazine,* and *temozolomide*. Specific adverse reactions include irreversible pulmonary fibrosis due to busulfan and hemorrhagic cystitis caused by the cyclophosphamide metabolite acrolein (preventable by the uro-protectant mesna = sodium 2-mercaptoethane sulfonate). The **platinum-containing compounds** *cisplatin, carboplatin,* and *oxaliplatin* release platinum, which binds to DNA.

Cystostatic antibiotics insert themselves into the DNA double strand; this may lead to strand breakage (e.g., with *bleomycin).* The *anthracycline antibiotics daunorubicin* and *doxorubicin (Adriamycin)* may induce cardiomyopathy. Bleomycin can also cause pulmonary fibrosis. *Epirubicin* and *idarubicin* were developed in order to reduce the cardiotoxicity. *Trabectin,* which also inserts itself into the DNA double strand, is not an antibiotic; it is obtained from a sea squirt. Mitoxantrone and pixantrone are other agents.

Induction of strand breakage may result from inhibition of topoisomerase. **The epipodophyllotoxins** *etoposide* and *teniposide* interact with topoisomerase II, which functions to split, transpose, and reseal DNA strands; these agents cause strand breakage by inhibiting resealing. The "tecans" *topotecan* and *irinotecan* are derivatives of camptothecin from the fruits of a Chinese tree *(Camptotheca acuminata).* They inhibit topoisomerase I, which induces breaks in single-strand DNA.

► **Inhibition of nucleobase synthesis** (► **Fig. 35.22**). Tetrahydrofolic acid (THF) is required for the synthesis of both purine bases and thymidine. Formation of THF from folic acid involves dihydrofolate reductase (p. 272). The *folate analogue methotrexate* inhibits enzyme activity. Cellular stores of THF are depleted. The effect of these antimetabolites can be reversed by administration of folinic acid (5-formyl-THF, leucovorin, citrovorum factor). *Hydroxyurea (hydroxycarbamide)* inhibits ribonucleotide reductase that normally converts ribonucleotides into deoxyribonucleotides subsequently used as DNA building blocks.

► **Incorporation of false building blocks** (► **Fig. 35.23**). Unnatural nucleobases *(6-mercaptopurine; 5-fluorouracil)* and abnormal nucleosides with incorrect sugars (e.g., *cytarabine, gemcitabine),* an incorrect base (e.g., *cladribine)* or both (e.g., *fludarabine, capecitabine)* act as antimetabolites. They inhibit DNA/RNA synthesis or lead to synthesis of missense nucleic acids.

Azacitidine and *decitabine* appear to halt malignant growth by inhibiting DNA methyltransferase.

6-Mercaptopurine results from biotransformation of the inactive precursor *azathioprine* (formula in A3). The uricostatic *allopurinol* (p. 350) inhibits the degradation of 6-mercaptopurine such that coadministration of the two drugs requires dose reduction of the latter.

► **Combination therapy.** Cytostatics are frequently administered in complex therapeutic regimens designed to improve efficacy and tolerability of treatment.

► **Supportive therapy.** Cancer chemotherapy can be supported by adjunctive medications. The following are used to protect against vomiting induced by cytostatic drugs: (1) *dexamethasone* as a basic agent; (2) a 5-HT_3 antagonist like *ondansetron* (for early emesis), and (3) the NK_1 receptor antagonist *aprepitant,* which is effective against delayed emesis with onset after more than 24 hours. Bone marrow depression can be counteracted by granulocyte and granulocyte/macrophage colony-stimulating factors (filgrastim and lenograstim). Mucosal damage can be helped by *palifermin,* a keratinocyte growth factor.

A. Cytostatics: alkylating agents and cytostatic antibiotics (1), inhibitors of tetrahydrofolate synthesis (2), antimetabolites (3)

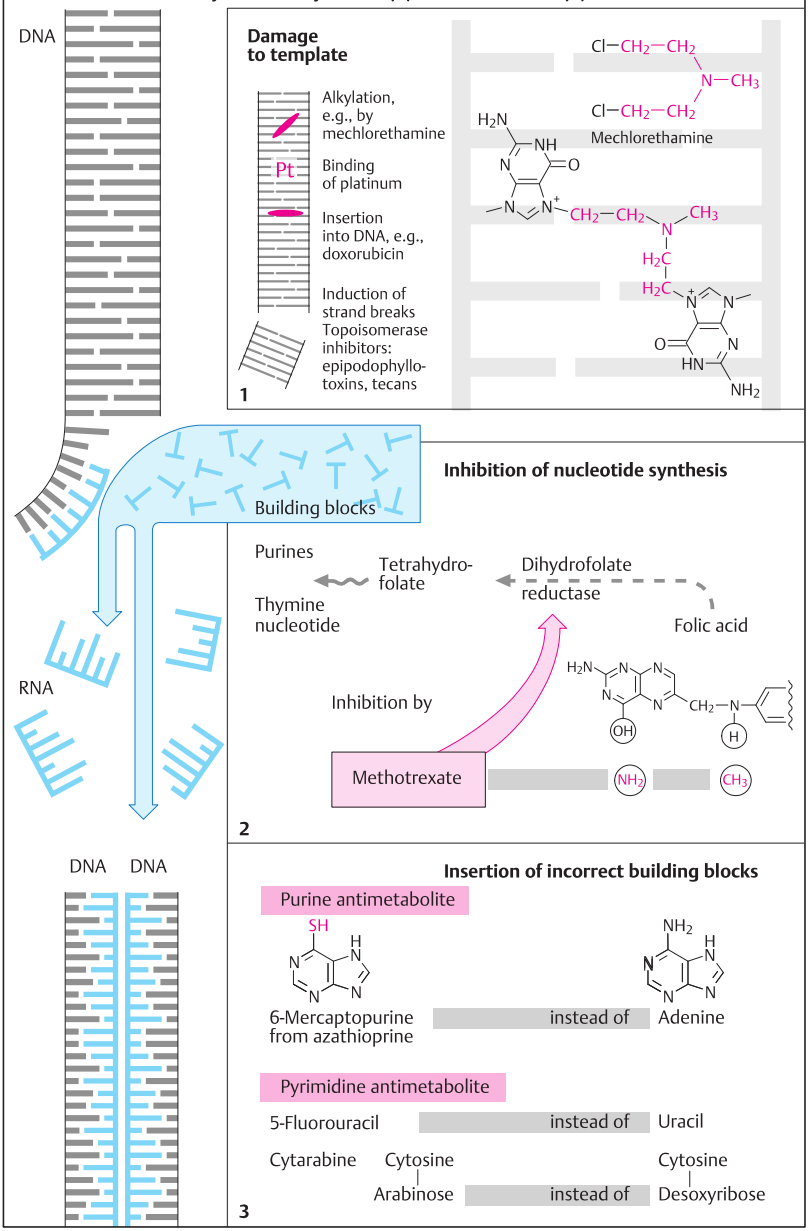


Fig. 35.2

Interference with Cell Proliferation Signaling Pathways

Even malignant cells require a good supply of nutrients. They obey physiological growth stimuli and make use of normal intracellular signaling pathways to control cell replication. It is possible to block these processes at various levels (▶ Fig. 35.3**A**).

The antibody *bevacizumab* is directed against vascular endothelial growth factor (VEGF). VEGF promotes the development of new blood vessels (see p. 302). Switching it off is intended to "starve" the neoplasm.

Growth factors are proteins that stimulate receptors located in the plasmalemma. These then form pairs (receptor dimerization) and on the cytosolic side of the plasmalemma tyrosine kinase activity is switched on, hence the name **receptor tyrosine kinases.** By "autophosphorylation" of certain tyrosine residues, the receptor becomes able to activate intracellular signaling molecules. A signal chain is set in motion that results in mitosis. **Cytoplasmic kinases** are incorporated in this signaling pathway. Depending on their preferred substrate, they are classified as *tyrosine kinases* and *serine/threonine kinases.*

The growth factor binding site of receptor tyrosine kinases can be blocked. This is achieved by *cetuximab* in the case of the HER1 subtype of the human epidermal growth factor receptor (HER) family (indication: colon cancer) and by *trastuzumab* in the HER2 subtype (indication: breast cancer, p. 302). The inhibitor *erlotinib* docks on the intracellular catalytic domain of HER1 (used in non-small-cell bronchial carcinoma). Unlike antibodies, these and the other kinase inhibitors are small molecules that can be given orally. *Sunitinib* has a broad inhibitory action against different receptor tyrosine kinases, including that of the VEGF receptor (indication, e.g., in renal cell carcinoma). The tyrosine kinase inhibitor *imatinib* (p. 302), which also inhibits certain receptor tyrosine kinases, is used to block intracellular kinases. *Sorafenib* is a nonspecific blocker of serine/threonine kinases (including raf-1) as well as cytoplasmic and receptor tyrosine kinases and is a reserve agent in renal cell carcinoma. ▶ Tables 47.1 and 47.2 list the antineoplastic antibodies and kinase inhibitors.

The time sequence of cell division processes requires correctly timed inactivation of signaling molecules. Phosphorylation can be reversed by phosphatases. Signaling molecules that are no longer needed can be broken down. Ubiquitin steers proteins to the proteasome for breakdown, where it is threaded into its catalytic channel and fragmented. The **proteasome inhibitor** *bortezomib* blocks proteolysis. Accumulation of proteins that have to be broken down leads to cell death (indication: multiple myeloma).

In multiple myeloma, thalidomide (notorious when used as a hypnotic in the past because of its teratogenic effect) inhibits cell proliferation, promotes apoptosis, blocks angiogenesis, and activates natural killer cells. The mechanism of action is unclear. At least with regard to the teratogenic effect it has been postulated that binding to DNA promoter regions with the sequence GGGCGG (GC boxes) inhibits gene expression. Lenalidomide and pomalidomide are related structurally and functionally to thalidomide.

Influencing **hormonal signaling pathways** is discussed elsewhere (e.g., GnRH superagonists for prostate carcinoma, p. 236; estrogen receptor antagonists and aromatase inhibitors in breast carcinoma, p. 254).

Immunological signaling pathways are used with *interferon alfa* for hairy cell leukemia and *interleukin-2 (aldesleukin)* for advanced renal cell carcinoma.

It should be noted that G-protein-coupled receptors may be involved in malignant growth as well as receptor tyrosine kinases. A **GPCR** named **smoothened** has a central role in the **hedgehog signaling pathway,** which is important for embryo development and cell differentiation. *Vismodegib* inhibits this receptor. Vismodegib is used orally to treat basal cell carcinoma of the skin. The substance is teratogenic so it is contraindicated in pregnancy.

A. Interference with cell proliferation signaling pathways

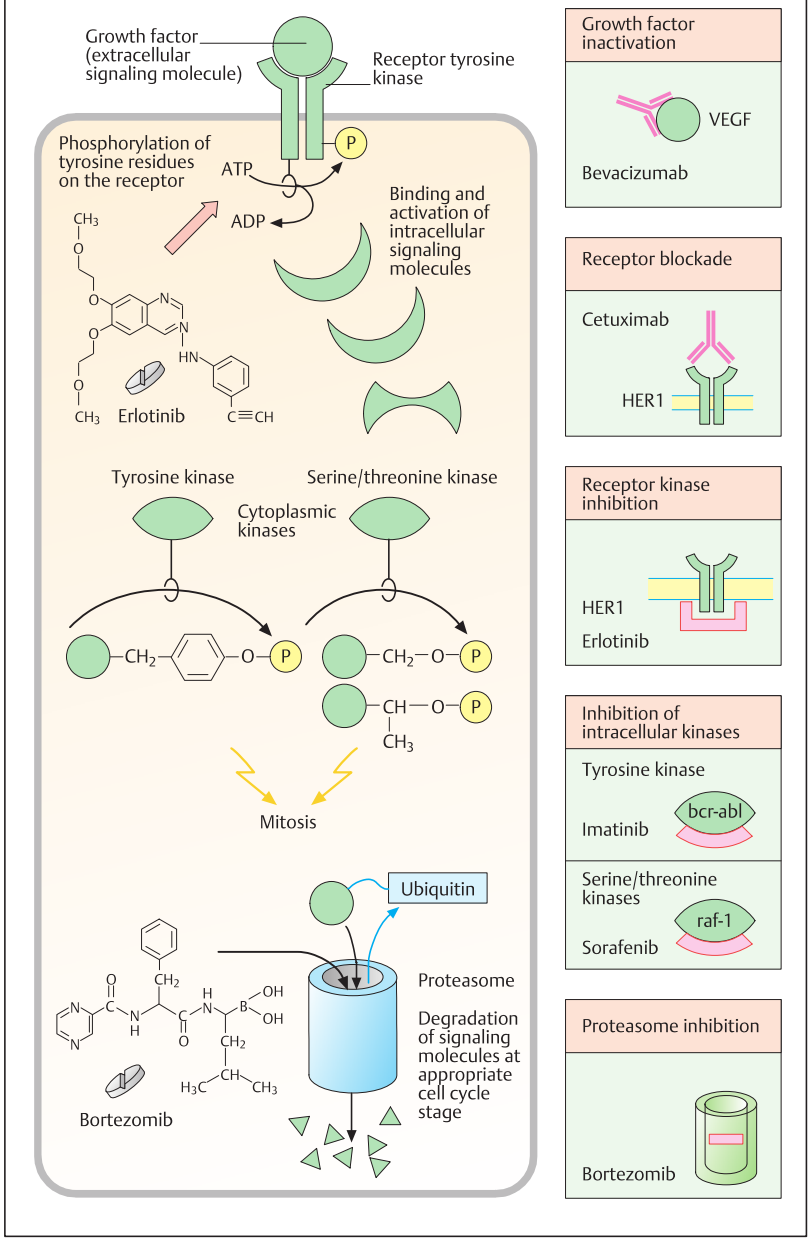


Fig. 35.3

Special Antineoplastic Drug Actions

When neoplastic cells display special metabolic properties *which are different from those of normal cells,* targeted pharmacotherapeutic intervention becomes possible (▶ Fig. 35.4**A**).

▶ **Imatinib.** Chronic myelogenous leukemia (CML) results from a genetic defect in the hematopoietic stem cells of the bone marrow. Nearly all CML patients possess the *Philadelphia chromosome.* It results from translocation between chromosomes 9 and 22 of the *c-abl* proto-oncogene, leading to the hybrid *bcr-abl* fusion gene on chromosome 22. The recombinant gene encodes a tyrosine kinase mutant with unregulated (constitutive), enhanced activity that promotes cell proliferation. Imatinib is a tyrosine kinase inhibitor that specifically affects this mutant but also interacts with some other kinases. It can be used orally in Philadelphia chromosome-positive CML.

Dasatinib and *nilotinib* are reserve drugs that can be used in the case of imatinib resistance.

Bevacizumab is an angiogenesis inhibitor that has been approved for the treatment of bowel and breast cancer and other neoplasms. A solid neoplasm needs an adequate blood supply in order to thrive. Signaling proteins from the vascular endothelial growth factor (VEGF) family can be produced by nearly all cells. An important stimulus for their release is reduced O_2 partial pressure, as occurs, for instance, at the middle of a solid tumor. VEGFs stimulate existing endothelial cells to proliferate. The new cells migrate, develop a lumen and so provide a connection between the neoplastic tissue and the blood supply. However, proper angiogenesis is also important for repair processes in inflammation and wound healing. This results in possible side effects: gastrointestinal perforation, hemorrhage, and also a rise in blood pressure (reduced endothelial NO production).

Ranibizumab, the Fab fragment of bevacizumab, is injected locally in the eye to treat neovascularization in wet macular degeneration.

Trastuzumab exemplifies a growing number of monoclonal antibodies that have become available for antineoplastic therapy. These are directed against cell surface proteins that are strongly expressed by cancer cells. Trastuzumab binds to HER2, the receptor for epidermal growth factor. The density of this receptor is greatly increased in some types of breast cancer. When the tumor cells have bound antibody, immune cells can recognize them as elements to be eliminated. Trastuzumab is indicated in advanced cases under certain conditions. The antibody is cardiotoxic; it is likely that cardiomyocytes also express HER2. HER2 is a receptor tyrosine kinase. It should be mentioned that the tyrosine kinase domain of the receptor protein that faces the interior of the cell can also be inhibited by *lapatinib.*

Mechanisms of Resistance to Cytostatics

Initial success can be followed by loss of effect because of the emergence of resistant tumor cells. Mechanisms of resistance are multifactorial (▶ Fig. 35.4**B**).

- *Diminished cellular uptake* may result from reduced synthesis of a transport protein that may be needed for membrane penetration (e.g., methotrexate).
- *Augmented drug extrusion:* increased synthesis of the P-glycoprotein that extrudes drugs from the cell (e.g., anthracyclines, vinca alkaloids, epipodophyllotoxins, and paclitaxel) is responsible for multidrug resistance (*mdr1* gene amplification).
- *Diminished bioactivation of a prodrug,* e.g., cytarabine, which requires intracellular phosphorylation to become cytotoxic.
- *Change in site of action:* e.g., increased synthesis of dihydrofolate reductase may occur as a compensatory response to methotrexate.
- *Damage repair:* DNA repair enzymes may become more efficient in repairing defects caused by cisplatin. Inhibition of apoptosis due to activation of antiapoptotic cellular mechanisms.

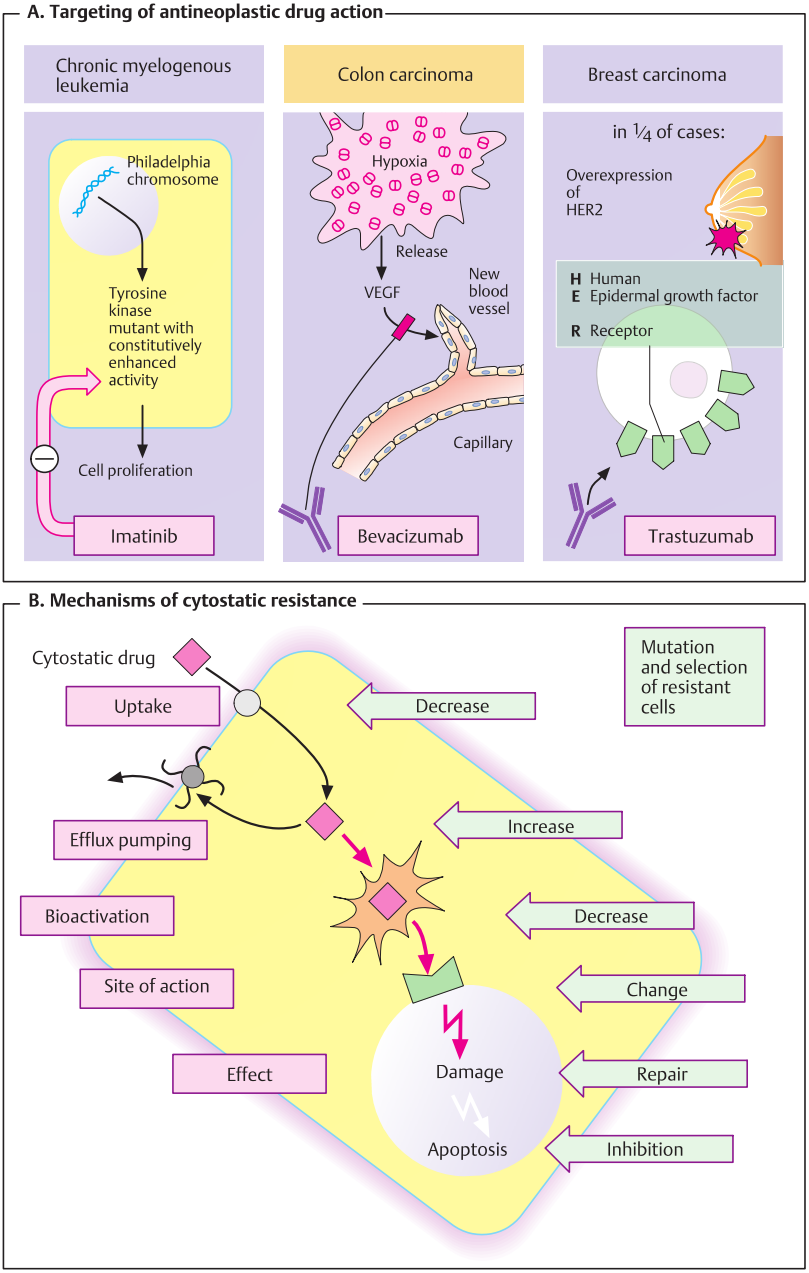

A. Targeting of antineoplastic drug action
Chronic myelogenous leukemia
Philadelphia chromosome
Tyrosine kinase mutant with constitutively enhanced activity
Cell proliferation
Imatinib
Colon carcinoma
Hypoxia
Release
VEGF
New blood vessel
Capillary
Bevacizumab
Breast carcinoma
in ¼ of cases:
Overexpression of HER2
H Human
E Epidermal growth factor
R Receptor
Trastuzumab
B. Mechanisms of cytostatic resistance
Cytostatic drug
Uptake
Efflux pumping
Bioactivation
Site of action
Effect
Damage
Apoptosis
Decrease
Increase
Decrease
Change
Repair
Inhibition
Mutation and selection of resistant cells

Fig. 35.4

Inhibition of Immune Responses

Both the prevention of *transplant rejection* and the treatment of *autoimmune disorders* call for a suppression of immune responses. However, immune suppression also entails weakened defenses against infectious pathogens and a long-term increase in the risk of neoplasms.

A specific **immune response** begins with the binding of antigen by lymphocytes carrying specific receptors with the appropriate antigen-binding site. B-lymphocytes "recognize" antigen surface structures by means of membrane receptors that resemble the antibodies formed subsequently. T-lymphocytes (and naive B cells) require the antigen to be presented on the surface of macrophages or other cells in conjunction with the major histocompatibility complex (MHC); the latter permits recognition of antigenic structures by means of the T-cell receptor. T-helper (T_H) cells carry adjacent CD3 and CD4 complexes, cytotoxic T cells a CD8 complex. The CD proteins assist in docking to the MHC. T-cell activation is also increased by contact with other membrane proteins: CD 80/86 in the case of the antigen-presenting cell and CD 28 on the lymphocyte. There is a built-in physiological brake as the activated lymphocyte releases CD28-like "dummy" molecules into the extracellular space; these "cap" the CD 80/86 complex and block it from making contact with and activating the lymphocyte. This dummy molecule is named CTLA-4. Besides recognition of antigen, stimulation by cytokines plays an essential part in the activation of lymphocytes. Interleukin-1 is formed by macrophages, and various interleukins (IL), including IL-2, are made by T-helper cells. As antigen-specific lymphocytes proliferate, immune defenses are set into motion.

▶ **Interference with antigen recognition. Glatiramer acetate** consists of peptides of varying lengths, polymerized in random sequence from the amino acids glutamine, lysine, alanine, and tyrosine. It can be used in the treatment of multiple sclerosis besides β-interferon. This disease is caused by a T-lymphocyte-mediated autoaggression directed against oligodendrocytes that form myelin sheaths of CNS axons. The culprit antigen appears to be myelin basic protein. Glatiramer resembles the latter; by blocking antigen receptors, it interferes with antigen recognition by lymphocytes.

Abatacept is a fusion protein consisting of the lymphocyte CD 28 dummy molecule CTLA-4 and an antibody Fc fragment. It imitates the physiological brake of antigen-mediated T-cell stimulation and is used in rheumatoid arthritis (p. 360). The similarly constructed belatacept is used for immunosuppression following kidney transplantation.

▶ **Inhibition of cytokine production and action. Glucocorticoids** modulate the expression of numerous genes; thus, the production of IL-1 and IL-2 is inhibited, which explains the suppression of T-cell-dependent immune responses. In addition, glucocorticoids interfere with inflammatory cytokines and signaling molecules at various other sites. Glucocorticoids are used in organ transplantations, autoimmune diseases, and allergic disorders. Systemic use carries the risk of iatrogenic Cushing syndrome (p. 242).

Ciclosporin and related substances inhibit the production of cytokines, in particular interleukin-2. In contrast to glucocorticoids, the plethora of accompanying metabolic effects is absent (see the section on calcineurin inhibitors, p. 306, for more details).

Anakinra is a recombinant form of an endogenous antagonist at the interleukin-1 receptor; it is used in rheumatoid arthritis (p. 360).

Basiliximab is a monoclonal antibody against the receptor for IL-2. It consists of murine Fab fragments and a human Fc-segment. It is used to suppress transplant rejection reactions. Tocilizumab (p. 360) and ustekinumab (p. 378) are other interleukin inhibitors.

▶ **Disruption of cell metabolism with inhibition of proliferation.** At dosages below those needed to treat malignancies, some cytostatics are also employed for immunosuppression; e.g., azathioprine, methotrexate, and cyclophosphamide. The antiproliferative effect is not specific for lymphocytes and involves both T and B cells.

Mycophenolate mofetil has a more specific effect on lymphocytes than on other cells. It inhibits inosine monophosphate dehydrogenase, which catalyzes purine synthesis in lymphocytes. It is used in acute tissue rejection responses.

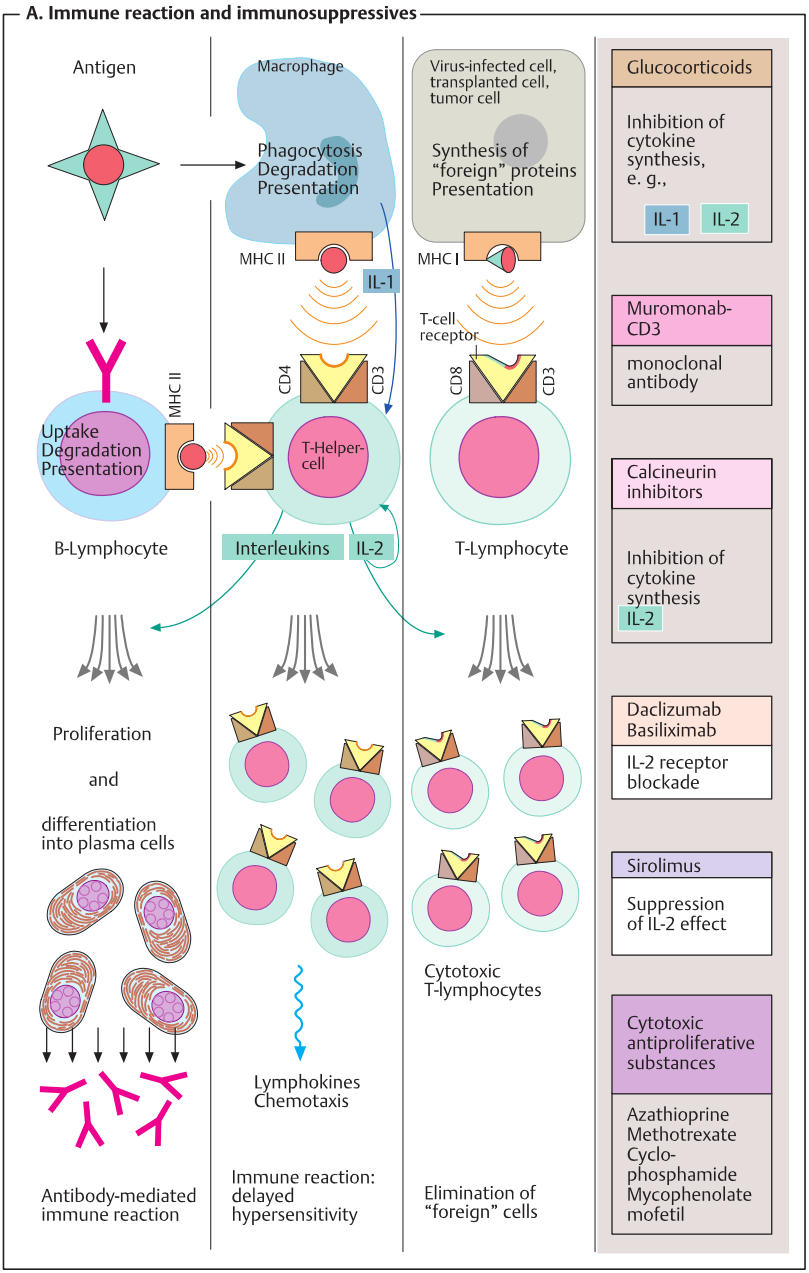

A. Immune reaction and immunosuppressives
Antigen
Macrophage
Phagocytosis
Degradation
Presentation
Virus-infected cell, transplanted cell, tumor cell
Synthesis of "foreign" proteins
Presentation
MHC II
MHC I
IL-1
T-cell receptor
CD4
CD3
CD8
CD3
MHC II
Uptake
Degradation
Presentation
T-Helper-cell
B-Lymphocyte
Interleukins
IL-2
T-Lymphocyte
Proliferation
and
differentiation
into plasma cells
Cytotoxic
T-lymphocytes
Lymphokines
Chemotaxis
Antibody-mediated immune reaction
Immune reaction: delayed hypersensitivity
Elimination of "foreign" cells
Glucocorticoids
Inhibition of cytokine synthesis, e. g.,
IL-1
IL-2
Muromonab-CD3
monoclonal antibody
Calcineurin inhibitors
Inhibition of cytokine synthesis
IL-2
Daclizumab
Basiliximab
IL-2 receptor blockade
Sirolimus
Suppression of IL-2 effect
Cytotoxic antiproliferative substances
Azathioprine
Methotrexate
Cyclo-phosphamide
Mycophenolate mofetil

Fig. 36.1

Calcineurin Inhibitors, Sirolimus

Ciclosporin (▶ Fig. 36.2A) is of fungal origin; it is a peptide composed of 11, in part atypical, amino acids. Therefore, orally administered ciclosporin is not degraded by gastrointestinal proteases. In T-helper cells, it *inhibits the production of interleukin-2* by interfering at the level of transcriptional regulation. Normally, "nuclear factor of activated T cells," (NFAT) promotes the expression of interleukin-2. This requires dephosphorylation of the *precursor*, phosphorylated NFAT, by the *phosphatase calcineurin*, enabling NFAT to enter the cell nucleus from the cytosol. Ciclosporin binds to the protein *cyclophilin* in the cell interior; the complex inhibits calcineurin, hence the production of interleukin-2.

The breakthroughs in *modern transplantation medicine* are largely attributable to the introduction of ciclosporin. It is now also employed in certain autoimmune diseases, atopic dermatitis, and other disorders.

The predominant adverse effect of ciclosporin is *nephrotoxicity*. Its dosage must be titrated so that blood levels are neither too high (risk of renal injury) nor too low (rejection reaction). To complicate the problem, ciclosporin is a substance difficult to manage therapeutically. Oral bioavailability is incomplete. Back-transport of the drug into the gut lumen occurs via the p-glycoprotein efflux pump, in addition to metabolism by cytochrome oxidases of the 3A subfamily. Hepatic CYP3A4 enzymes contribute to presystemic elimination and are responsible for elimination of systemically available ciclosporin. Diverse drug interactions may occur by interference with CYP3A and p-glycoprotein. For optimal dosage adjustment, *monitoring of plasma levels* is mandatory.

Drug-mediated suppression of transplant rejection entails long-term treatment. Protracted immunosuppression carries an increased risk of malignant tumors. Risk factors for cardiovascular diseases may be adversely affected—a critical and important concern in long-term prognosis.

Tacrolimus is a macrolide antibiotic from *Streptomyces tsukubaensis*. In principle, it acts like ciclosporin. At the molecular level, however, its "receptor" is not cyclophilin but a so-called FK-binding protein. Tacrolimus is likewise used to prevent allograft rejection. Its epithelial penetrability is superior to that of ciclosporin, allowing topical application in atopic dermatitis.

Sirolimus (rapamycin, ▶ Fig. 36.2A) is another macrolide, produced by *Streptomyces hydroscopicus*. Its immunosuppressant action does not appear to involve inhibition of calcineurin. It forms a complex with the FK protein, imparting a special conformation to it; and the complex then inhibits the mTOR (mammalian target of rapamycin) phosphatase. The latter operates in the signaling path leading from the interleukin-2 receptor to activation of mitosis in lymphocytes. Thus, sirolimus inhibits lymphocyte proliferation. It is approved for the prevention of transplant rejection.

The structure and action of *everolimus* resemble those of sirolimus. Sirolimus is also used to coat stents that are placed in atherosclerotic coronary arteries to maintain vessel patency following balloon dilation. Sirolimus is intended to halt proliferation processes in the vessel wall that would lead to narrowing of the lumen. The related *temsirolimus* is used in the treatment of renal cell carcinoma.

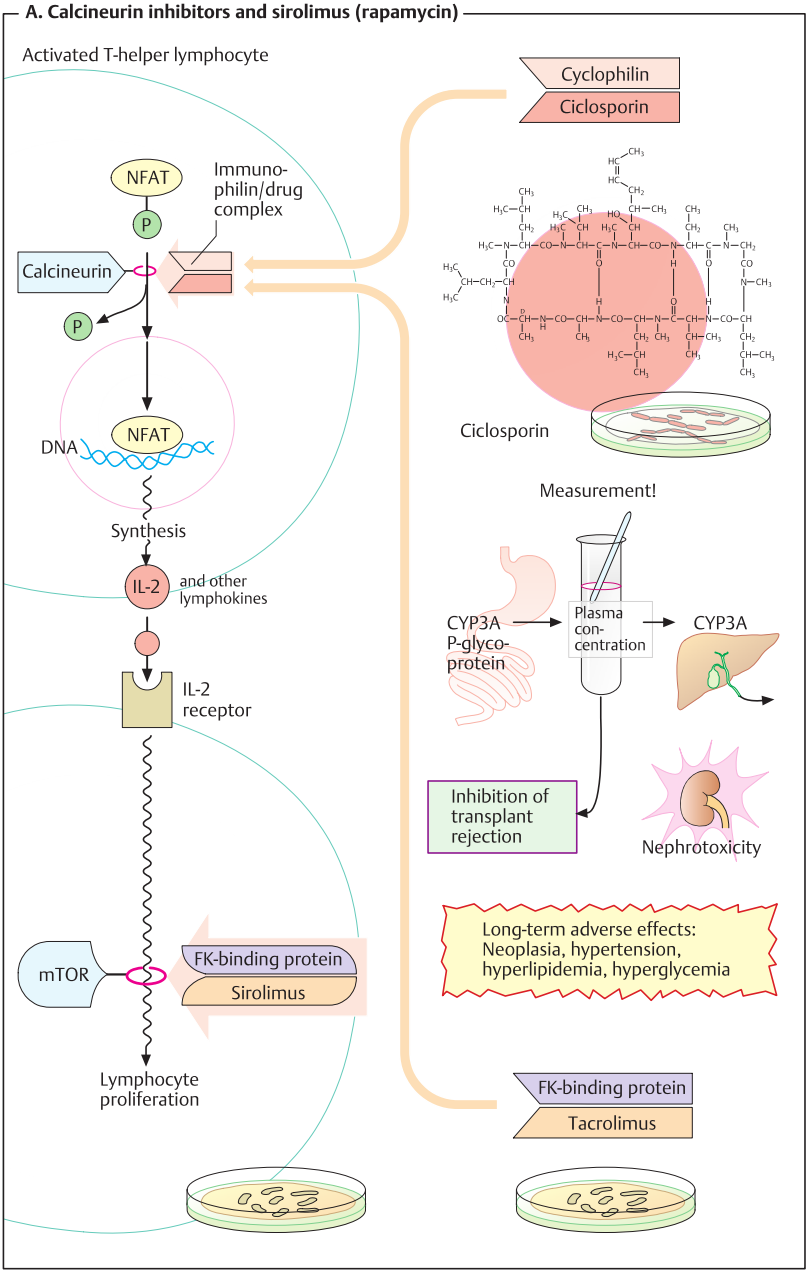

A. Calcineurin inhibitors and sirolimus (rapamycin)
Activated T-helper lymphocyte
NFAT
P
Immuno-
philin/drug
complex
Calcineurin
P
DNA
NFAT
Synthesis
IL-2
and other
lymphokines
IL-2
receptor
mTOR
FK-binding protein
Sirolimus
Lymphocyte
proliferation
Cyclophilin
Ciclosporin
Ciclosporin
Measurement!
CYP3A
P-glyco-
protein
Plasma
con-
centration
CYP3A
Inhibition of
transplant
rejection
Nephrotoxicity
Long-term adverse effects:
Neoplasia, hypertension,
hyperlipidemia, hyperglycemia
FK-binding protein
Tacrolimus

Fig. 36.2

Antidotes and Treatment of Poisoning

Drugs used to counteract drug overdosage are considered under the appropriate headings; e.g., physostigmine with atropine; naloxone with opioids; flumazenil with benzodiazepines; antibody (Fab fragments) with digitalis; and *N*-acetylcysteine with acetaminophen intoxication.

Chelating agents (▶ Fig. 37.1) serve as antidotes in poisoning with heavy metals. They act to complex and, thus, "inactivate" heavy metal ions. Chelates (from Greek: *chele* = pincer [of crayfish]) represent complexes between a metal ion and molecules that carry several binding sites for the metal ion. Because of their high affinity, chelating agents "attract" metal ions present in the organism. The chelates are nontoxic, are excreted predominantly via the kidney, and maintain a tight organometallic bond in the concentrated, usually acidic, milieu of tubular urine and thus promote the elimination of metal ions.

Na_2Ca-EDTA (▶ Fig. 37.1**A**) is used to treat lead poisoning. This antidote cannot penetrate through cell membranes and must be given parenterally. Because of its high binding affinity, the lead ion displaces Ca^{2+} from its bond. The lead-containing chelate is eliminated renally. Nephrotoxicity predominates among the unwanted effects. **Na_3Ca-pentetate** is a complex of diethylenetriaminopentaacetic acid (DPTA) and serves as antidote in lead and other metal intoxications.

Dimercaprol (BAL, British Anti-Lewisite) was developed in World War II as an antidote against vesicant organic arsenicals (▶ Fig. 37.1**B**). It is able to chelate various metal ions. A related compound, both in terms of structure and activity, is **dimercaptopropanesulfonic acid,** the sodium salt of which is suitable for oral administration. Shivering, fever, and skin reactions are potential adverse effects.

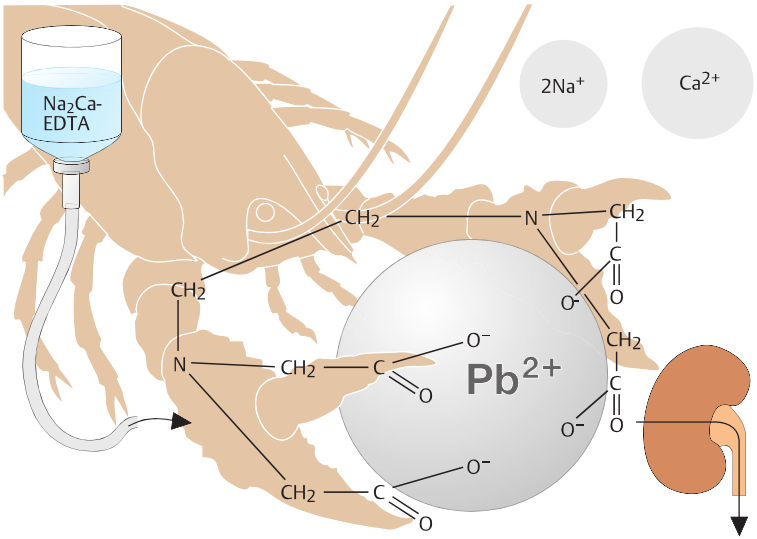
Deferoxamine derives from *Streptomyces pilosus.* The substance possesses a very high iron-binding capacity but does not withdraw iron from hemoglobin or cytochromes. It is poorly absorbed enterally and must be given parenterally to cause increased excretion of iron. Oral administration is indicated only if enteral absorption of iron is to be curtailed. Unwanted effects include allergic reactions. The new deferasirox can be given orally.

It should be noted that bloodletting is the most effective means of removing iron from the body; however, this method is unsuitable for treating conditions of iron overload associated with anemia.

D-Penicillamine can promote the elimination of copper (e.g., in Wilson disease) and of lead ions. It can be given orally. Two additional indications are cystinuria and rheumatoid arthritis. In cystinuria, formation of cystine stones in the urinary tract is prevented because the drug can form a disulfide with cysteine that is readily soluble. In rheumatoid arthritis (p. 360), penicillamine can be used as a disease-modifying agent. The therapeutic effect may result in part from a reaction with aldehydes, whereby polymerization of collagen molecules into fibrils is inhibited. Unwanted effects are cutaneous damage (p. 92) with diminished resistance to mechanical stress with a tendency to form blisters, nephrotoxicity, bone marrow depression, and taste disturbances.

Apart from specific antidotes (if they exist), the treatment of poisoning also calls for **symptomatic measures** (control of blood pressure and blood electrolytes; monitoring of cardiac and respiratory function; prevention of toxin absorption by activated charcoal). An important step is early emptying of the stomach by gastric lavage and, if necessary, administration of an osmotic laxative. Use of emetics is inadvisable. If an emetic must be given, ipecac syrup would be the first choice. Saturated salt solution p.o. and apomorphine s.c. are hazardous.

A. Chelation of lead ions by EDTA



EDTA: ethylenediamine tetra acetate

B. Chelators

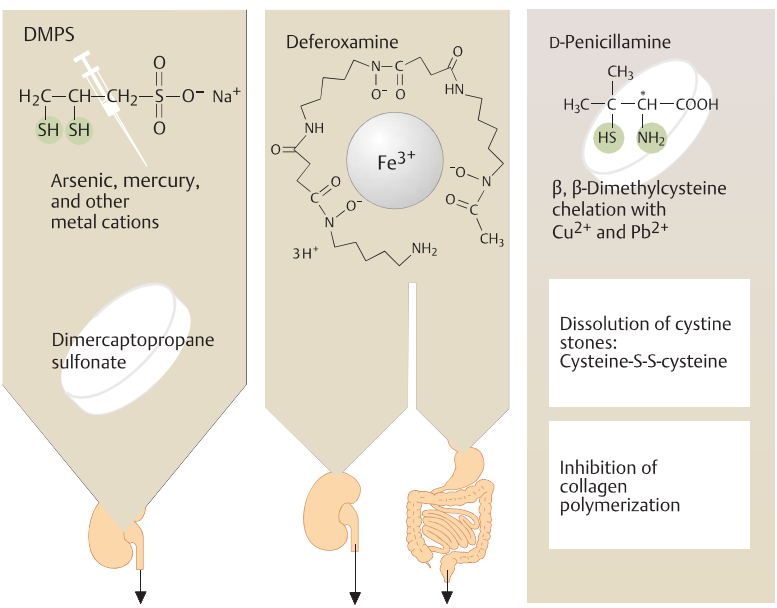


Fig. 37.1

► **Reactivators of phosphorylated acetylcholinesterase (AChE).** Certain organic phosphoric acid compounds bind with high affinity to a serine OH group in the active center of AChE and thus block the hydrolysis of acetylcholine. As a result, the organism is poisoned with its own transmitter substance, acetylcholine. This mechanism operates not only in humans and warm-blooded animals but also in lower animals, ACh having been "invented" early in evolution. Thus, **organophosphates** enjoy widespread application as insecticides. Time and again, their use has led to human poisoning because these toxicants can enter the body through the intact skin or inhaled air. Depending on the severity, signs of poisoning include excessive parasympathetic tone, ganglionic blockade, and inhibition of neuromuscular transmission leading to peripheral respiratory paralysis. Specific treatment of the intoxication consists in administration of extremely high doses of *atropine* and reactivation of acetylcholinesterase with *pralidoxime* or *obidoxime* (► Fig. 37.2**A**).

Unfortunately, the organophosphates have been misused as biological weapons. In World War II, they were stockpiled on both sides but not deployed. The efficacy of the poisons was subsequently "demonstrated" in smaller local armed conflicts in developing countries. In the present global situation, the fear has arisen that organophosphates may be used by terrorist groups. Thus, understanding the signs of poisoning and the principles of treatment are highly important.

► **Tolonium chloride (toluidine blue).** Brown-colored methemoglobin, containing trivalent instead of divalent iron, is incapable of carrying O_2. Under normal conditions, methemoglobin is produced continuously, but reduced again with the help of glucose-6-phosphate dehydrogenase. Substances that promote formation of methemoglobin (► Fig. 37.2**B**) may cause a lethal deficiency of O_2. Tolonium chloride is a redox dye that can be given i.v. to reduce methemoglobin.

► **Antidotes for cyanide poisoning (► Fig. 37.2B).** Cyanide ions (CN^-) enter the organism in the form of hydrocyanic acid (HCN); the latter can be inhaled, released from cyanide salts in the acidic stomach juice, or enzymatically liberated from bitter almonds in the gastrointestinal tract. The lethal dose of HCN can be as low as 50 mg. CN^- binds with high affinity to trivalent iron and thereby arrests utilization of oxygen via mitochondrial cytochrome oxidases of the respiratory chain. Internal asphyxiation *(histotoxic hypoxia)* ensues while erythrocytes remain charged with O_2 (venous blood colored bright red).

In small amounts, cyanide can be converted to the relatively nontoxic thiocyanate (SCN^-) by hepatic "rhodanese" or sulfur-transferase. As a **therapeutic measure,** *sodium thiosulfate* can be given i.v. to promote formation of thiocyanate, which is eliminated in urine. However, this reaction is slow in onset. A more effective emergency treatment is the i.v. administration of the methemoglobin-forming agent *4-dimethylaminophenol,* which rapidly generates trivalent iron from divalent iron in hemoglobin. Competition between methemoglobin and cytochrome oxidase for CN^- ions favors the formation of cyanmethemoglobin. Hydroxycobalamin (= vitamin B_{12a}) is an alternative, very effective antidote because its central cobalt atom binds CN^- with high affinity to generate cyanocobalamin (= vitamin B_{12}).

Ferric ferrocyanide ("Prussian blue") is used to treat poisoning with thallium salts (e.g., in rat poison), initial symptoms of which are gastrointestinal disturbances, followed by nerve and brain damage, as well as hair loss. Thallium ions present in the organism are secreted into the gut but undergo reabsorption. The insoluble, nonabsorbable colloidal Prussian blue binds thallium ions. It is given orally to prevent absorption of acutely ingested thallium or to promote clearance from the organism by intercepting thallium that is secreted into the intestines (► Fig. 37.2**B**).

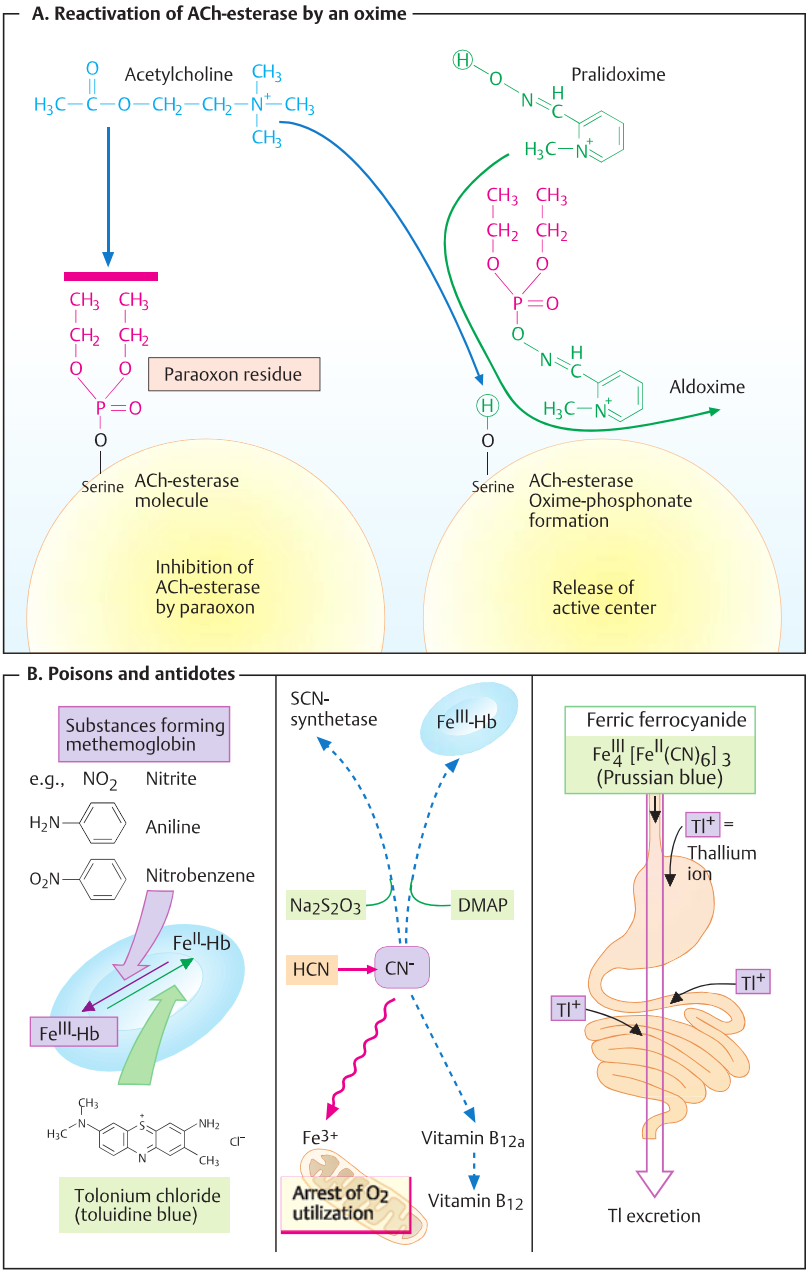

A. Reactivation of ACh-esterase by an oxime
Acetylcholine
Pralidoxime
Paraoxon residue
Aldoxime
Serine
ACh-esterase molecule
Inhibition of ACh-esterase by paraoxon
Serine
ACh-esterase Oxime-phosphonate formation
Release of active center
B. Poisons and antidotes
Substances forming methemoglobin
e.g., NO2 Nitrite
Aniline
Nitrobenzene
FeII-Hb
FeIII-Hb
Tolonium chloride (toluidine blue)
SCN-synthetase
FeIII-Hb
Na2S2O3
DMAP
HCN
CN-
Fe3+
Vitamin B12a
Vitamin B12
Arrest of O2 utilization
Ferric ferrocyanide
FeIII4 [FeII(CN)6] 3
(Prussian blue)
Tl+ = Thallium ion
Tl+
Tl+
Tl excretion

Fig. 37.2

Psychotomimetics (Psychedelics, Hallucinogens)

Psychotomimetics are able to elicit psychic changes like those manifested in the course of a psychosis, such as **illusionary distortion of perception** and **hallucinations.** This experience may be dreamlike in character; its emotional or intellectual transposition appears incomprehensible to the outsider.

A psychotomimetic effect is pictorially recorded in the series of portraits drawn by an artist under the influence of lysergic acid diethylamide (LSD). As the intoxicated state waxes and wanes wavelike, he reports seeing the face of the portrayed subject turn into a grimace, phosphoresce bluish-purple, and fluctuate in size as if viewed through a moving zoom lens, creating the illusion of abstruse changes in proportion and grotesque motion sequences. The diabolic caricature is perceived as threatening (▶ Fig. 38.1**A**).

Illusions also affect the senses of hearing and smell; sounds are "experienced" as floating beams and visual impressions as odors ("synesthesia"). Intoxicated individuals see themselves temporarily from the outside and pass judgment on themselves and their condition. The boundary between self and the environment becomes blurred. An elating sense of being one with the other and the cosmos sets in. The sense of time is suspended; there is neither past nor future. Objects are seen that do not exist, and experiences are felt that transcend explanation, hence the term "psychedelic" (Greek *delosis* = revelation) implying expansion of consciousness.

Naturally occurring hallucinogens are: *psilocin, psilocybin* (from the *Psilocybe mexicana* mushroom), *bufetonin* (the cutaneous gland secretion of a toad), and *mescaline* (from the Mexican cactus *Anhalonium lewinii* = peyote).

▶ **Cannabinoids.** Hashish, a resin obtained from Indian hemp, is a widespread drug that contains Δ^9-tetrahydrocannabinol (THC) as active substance. Hashish often acts as an **"entry-level" drug for hard drugs.** After using hashish, symptoms similar to those described above for LSD occur. Two specific binding sites have been found for tetrahydrocannabinol: CB_1 receptors in the CNS and CB_2 receptors in peripheral tissues. It is noteworthy that endogenous ligands have been discovered that act as agonists at CB receptors; these are **anandamide** and **2-arachnidonylglycerol.** These endocannabinoids are arachidonic acid derivatives. There has been intensive research into their physiological significance. An extract from the cannabis plant containing Δ^9-tetrahydrocannabinol and cannabidiol is available to treat spasticity in patients with multiple sclerosis. It is subject to controlled drug prescribing regulations. Blockade of CB_1 receptors by means of rimonabant to reduce appetite and aid weight loss was unsuccessful as the incidence of suicide increased. Endogenous cannabinoids appear to contribute to a sense of well-being.

In addition, other substances that do not act as primary hallucinogens, such as **amphetamine** derivatives (e.g., 3,4-dimethyl-dioxymethamphetamine = ecstasy and more recently 1-benzylpiperazine) and **cocaine,** are dangerous. Acute intoxication is associated with a misperception of reality, and a period of exhaustion follows. After prolonged use, dependence develops, associated with physical and intellectual decay. Withdrawal therapy is very difficult.

Psychotomimetics are devoid of therapeutic value; however, since their use leads to toxic effects and permanent damage, their manufacture and commercial distribution are prohibited (Schedule I, Controlled Drugs).

A. Psychotomimetic effect of LSD in a portrait artist

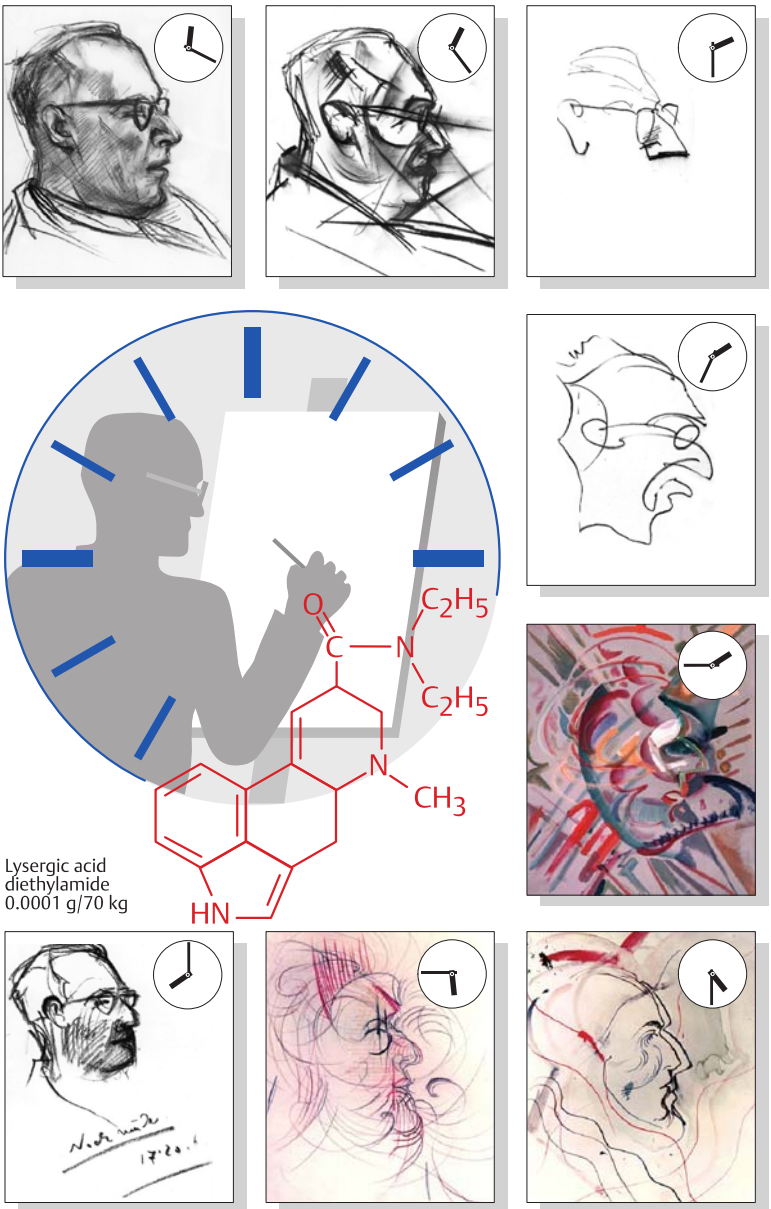


Fig. 38.1

Nicotine

Actions of Nicotine

Acetylcholine (ACh) is a mediator in the ganglia of the sympathetic and parasympathetic divisions of the autonomic nervous system. Here, ACh receptors are considered that are activated by nicotine (nicotinic receptors; NAChR, p. 120) and that play a leading part in fast ganglionic neurotransmission. These receptors represent ligand-gated ion channels (p. 82). Opening of the ion pore induces Na^+ influx followed by membrane depolarization and excitation of the cell. NAChR tend to desensitize rapidly; that is, during prolonged occupation by an agonist the ion pore closes spontaneously and cannot reopen until the agonist detaches itself.

Localization of Nicotinic ACh Receptors

Autonomic nervous system (▶ Fig. 38.2A, middle). In analogy to autonomic ganglia, NAChR are found also on epinephrine-releasing cells of the adrenal medulla, which are innervated by sympathetic first neurons. At all these synapses, the receptor is located postsynaptically in the somatodendritic region of the gangliocyte.

Motor end plate. Here the ACh receptors are of the *motor type.*

Central nervous system (CNS; ▶ Fig. 38.2A, top). NAChR are involved in various functions. They have a predominantly presynaptic location and promote transmitter release from axon terminals by means of depolarization. Together with ganglionic NAChR they belong to the *neuronal type,* which differs from the motor type in terms of the composition of its five subunits.

Effects of Nicotine on Body Function

Nicotine served as an experimental tool for the classification of acetylcholine receptors. As a tobacco alkaloid, nicotine is employed daily by a vast part of the human race for the enjoyment of its central stimulant action. Nicotine activates the brain's reward system, thereby promoting dependence. Regular use leads to habituation, which is advantageous in some respects (e.g., stimulation of the area postrema). In habituated subjects, cessation of nicotine use results in mainly psychological withdrawal symptoms (increased nervousness, lack of concentration). Prevention of these is an additional important incentive for continuing nicotine use. Peripheral effects caused by stimulation of autonomic ganglia may be perceived as useful ("laxative" effect of the first morning cigarette). Sympathetic activation without corresponding physical exertion ("silent stress") may in the long-term lead to grave cardiovascular damage (p. 316).

Aids for Smoking Cessation

Administration of nicotine by means of skin patches, chewing gum, or nasal spray is intended to make it easier for the smoker to quit. The habit should be broken by a gradual reduction of the nicotine dose. Initially, this may happen; however, the long-term relapse rate is disappointingly high.

Bupropion (amfebutamone) shows structural similarities to amphetamine and inhibits neuronal reuptake of norepinephrine and dopamine. It is supposed to aid smokers in "kicking the habit," possibly because it evokes CNS effects resembling those of nicotine. The high relapse rate after stopping the drug and its substantial side effects put its therapeutic value in doubt.

Varenicline is a further option to support smoking cessation. This acts as a *partial agonist* at certain nicotine receptor subtypes ($\alpha_4\beta_2$). As a result, the nicotine receptors needed for "successful smoking" are occupied but have diminished intrinsic activity. Nicotine obtained from smoking is virtually without effect. Side effects are vomiting, sleep disorders, headaches, constipation, and suicidal thoughts. The success rate is low.

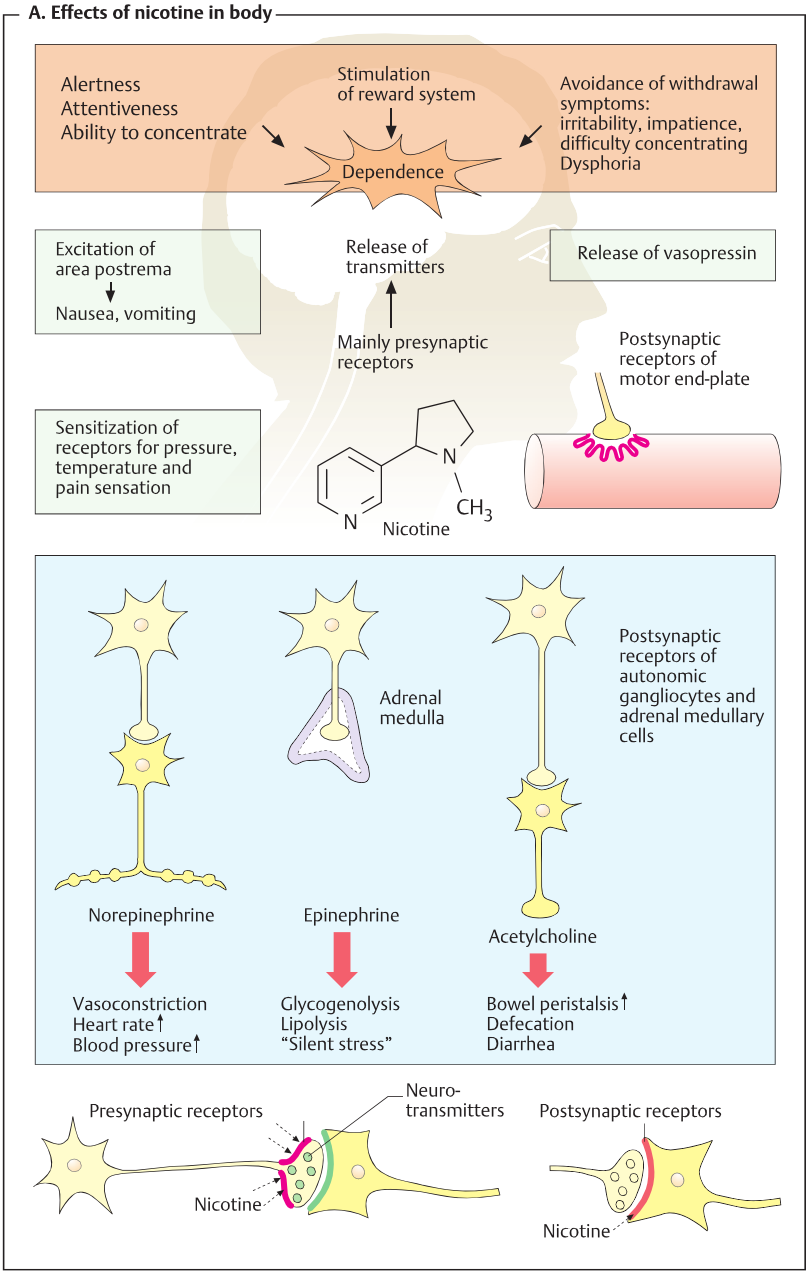

A. Effects of nicotine in body
Alertness
Attentiveness
Ability to concentrate
Stimulation of reward system
Dependence
Avoidance of withdrawal symptoms: irritability, impatience, difficulty concentrating Dysphoria
Excitation of area postrema
Nausea, vomiting
Release of transmitters
Mainly presynaptic receptors
Release of vasopressin
Postsynaptic receptors of motor end-plate
Sensitization of receptors for pressure, temperature and pain sensation
N
N
CH3
Nicotine
Adrenal medulla
Postsynaptic receptors of autonomic gangliocytes and adrenal medullary cells
Norepinephrine
Epinephrine
Acetylcholine
Vasoconstriction
Heart rate↑
Blood pressure↑
Glycogenolysis
Lipolysis
"Silent stress"
Bowel peristalsis↑
Defecation
Diarrhea
Presynaptic receptors
Neuro-transmitters
Postsynaptic receptors
Nicotine
Nicotine

Fig. 38.2

Consequences of Tobacco Smoking

The dried and cured leaves of the nightshade plant *Nicotiana tabacum* are known as tobacco. Tobacco is mostly smoked, less frequently chewed or taken as dry snuff. Combustion of tobacco generates ~4000 chemical compounds in detectable quantities. The xenobiotic burden on the smoker depends on a range of parameters, including tobacco quality, presence of a filter, rate and temperature of combustion, depth of inhalation, and duration of breath holding.

Tobacco contains 0.2–5% nicotine. In tobacco smoke, nicotine is present as a constituent of small tar particles. The amount of nicotine absorbed during smoking depends on the nicotine content, the size of membrane area exposed to tobacco smoke (N.B.: inhalation), and the pH of the absorbing surface. It is rapidly absorbed through bronchi and lung alveoli when present in free base form. However, protonation of the pyrrolidine nitrogen renders the corresponding part of the molecule hydrophilic and absorption is impeded. To maximize the yield of nicotine, tobaccos of some manufacturers are made alkaline. Smoking of a single cigarette produces peak plasma levels in the range of 25–50 ng/mL. When intake stops, nicotine concentration in plasma shows an initial rapid fall, due to distribution into tissues, and a terminal elimination phase with a half-life of 2 hours. Nicotine is degraded by oxidation.

The enhanced risk of **vascular disease** (coronary stenosis, myocardial infarction, and central and peripheral ischemic disorders, such as stroke and intermittent claudication) is likely to be a consequence of chronic exposure to nicotine. At the least, nicotine is under discussion as a factor favoring the progression of atherosclerosis. By releasing epinephrine, it elevates plasma levels of glucose and free fatty acids in the absence of an immediate physiological need for these energy-rich metabolites. Furthermore, it promotes platelet aggregability, lowers fibrinolytic activity of blood, and enhances coagulability.

The health risks of tobacco smoking are, however, attributable not only to nicotine but also to various other ingredients of tobacco smoke. Some of these possess demonstrable carcinogenic properties (e.g., the tobacco-specific nitrosoketone).

Dust particles inhaled in tobacco smoke, together with bronchial mucus, must be removed by the ciliated epithelium from the airways. However, ciliary activity is depressed by tobacco smoke and mucociliary transport is impaired. This favors bacterial infection and contributes to the chronic bronchitis associated with regular smoking (smoker's cough). Chronic injury to the bronchial mucosa could be an important causative factor in increasing the risk in smokers of death from bronchial carcinoma.

Statistical surveys provide an impressive correlation between the numbers of cigarettes smoked per day and the risk of death from coronary disease or lung cancer. On the other hand, statistics also show that, on cessation of smoking, the increased risk of death from coronary infarction or other cardiovascular disease declines over 5–10 years almost to the level of nonsmokers. Similarly, the risk of developing bronchial carcinoma is reduced.

Since most of the cigarette smoke is exhaled into the atmosphere, nonsmokers in enclosed spaces inhale "diluted smoke." It is now accepted that highly exposed **passive smokers** suffer from the same typical diseases as active smokers, though at statistically lower rates.

Smoking during pregnancy has negative effects on the embryo: birth weight is lower, perinatal mortality is increased, and postnatal development is delayed.

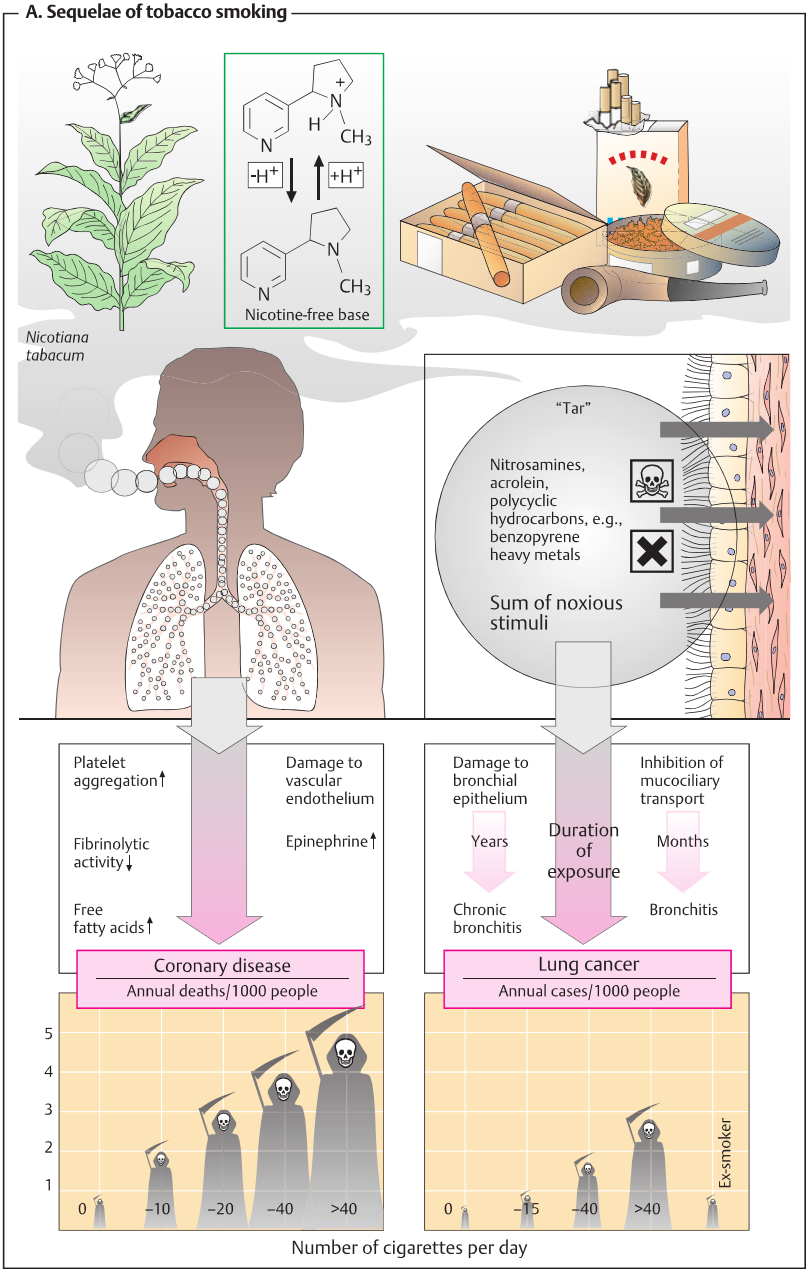

A. Sequelae of tobacco smoking
Nicotiana tabacum
Nicotine-free base
-H+
+H+
"Tar"
Nitrosamines, acrolein, polycyclic hydrocarbons, e.g., benzopyrene
heavy metals
Sum of noxious stimuli
Platelet aggregation
Fibrinolytic activity
Free fatty acids
Damage to vascular endothelium
Epinephrine
Damage to bronchial epithelium
Years
Chronic bronchitis
Duration of exposure
Inhibition of mucociliary transport
Months
Bronchitis
Coronary disease
Annual deaths/1000 people
Lung cancer
Annual cases/1000 people
5
4
3
2
1
0
–10
–20
–40
>40
0
–15
–40
>40
Ex-smoker
Number of cigarettes per day

Fig. 38.3

Alcohol Abuse

Since prehistoric times, ethanol-containing beverages have enjoyed widespread use as a recreational luxury. What applies to any medicinal substance also holds for alcohol: the dose alone makes the poison. Excessive, long-term consumption of alcoholic drinks, or **alcohol abuse**, is harmful to the affected individual. Alcoholism must be considered a grave disorder that plays a major role in terms of numbers alone; for instance, in the western world about 10% of the population are affected by this self-inflicted illness.

Ethanol is miscible with water and is well lipid-soluble, enabling it to penetrate easily through all barriers in the organism; the blood–brain barrier and the placental barrier are no obstacles. In liver cells, alcohol is broken down to acetic acid via acetaldehyde. Alcohol dehydrogenase can be blocked by the competitive inhibitor fomepizole. This action is utilized in ethylene glycol ($HO\text{-}CH_2\text{-}CH_2\text{-}OH$) poisoning as it halts the first step in its toxicity (▶ Fig. 38.4**A**). Ethyl alcohol is never ingested as a chemically pure substance but in the form of an alcoholic beverage that contains flavoring agents and higher alcohols, depending on its origin. The effect desired by the consumer takes place in the brain: ethanol acts as a stimulant, it disinhibits, and it enhances sociability, as long as the beverage is enjoyed in moderate quantities. After higher doses, self-critical faculties are lost and motor function is impaired—the familiar picture of the drunk. Still higher doses induce a comatose state (caution: hypothermia and respiratory paralysis). The complex effects on the CNS cannot be ascribed to a simple mechanism of action. An inhibitory effect on the NMDA subtype of glutamate receptor appears to predominate.

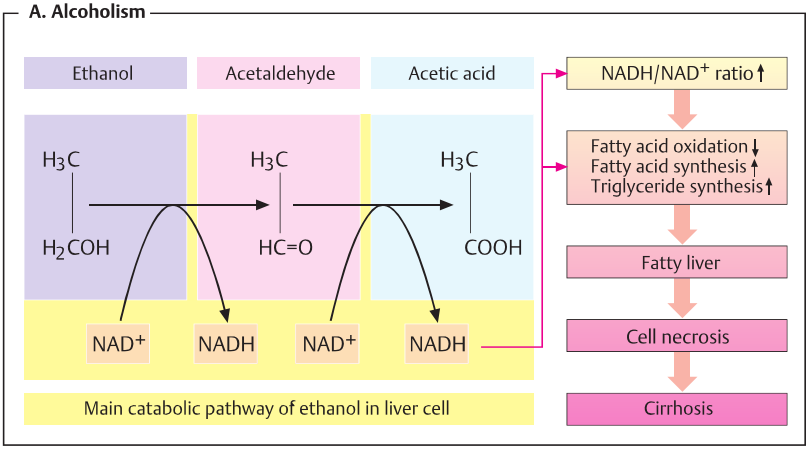
In chronic alcohol abuse, mainly two organs are damaged:

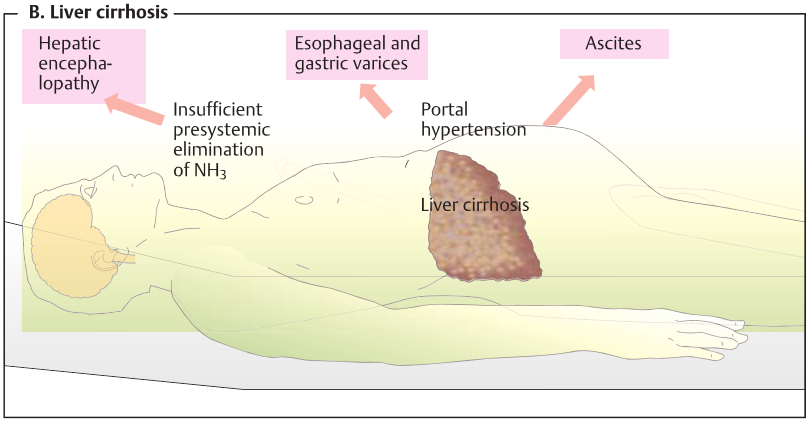
1. In the **liver,** hepatocytes may initially undergo fatty degeneration, this process being reversible. With continued exposure, liver cells die and are replaced by connective tissue newly formed from myofibroblasts: liver cirrhosis. Hepatic blood flow is greatly reduced; the organ becomes unable to fulfill its detoxification function (danger of hepatic coma). Collateral circulation routes develop (bleeding from esophageal varices) with production of ascites. Alcoholic liver cirrhosis is a severe, mostly progressive disease that permits only symptomatic therapy (▶ Fig. 38.4**B**).
2. The functional capacity of the **brain** is impaired. Irreversible damage may manifest in a measurable fallout of neuronal cell bodies. Often delirium tremens develops (usually triggered by alcohol withdrawal), which can be managed with intensive therapy (clomethiazole, haloperidol, among others). In addition, alcoholic hallucinations and Wernicke–Korsakott syndrome occur. All of these are desolate conditions.

Besides the liver and brain, other organs can be damaged by chronic excessive alcohol consumption: the peripheral nervous system develops polyneuropathy; gastritis occurs in the stomach, especially after consumption of drinks containing a high percentage of alcohol; the pancreas reacts with pancreatitis, the heart muscle with cardiomyopathy, and the kidney with nephritis.

It must be pointed out specifically that alcohol abuse during pregnancy leads to **embryo–fetal alcohol syndrome** (malformations, persistent intellectual deficit). This intrauterine intoxication is relatively common: one case per 1000 births (▶ Fig. 38.4**C**).

Chronic alcohol abuse is an expression of true dependence. Thus, **therapy of this addiction** is difficult and frequently without success. There is no pharmacotherapeutic silver bullet (the NMDA receptor antagonist *acamprosate* and the $GABA_B$ agonist *baclofen* may be worth trying). Above all, psychotherapeutic care, a change in milieu, and supportive treatment with benzodiazepines are important.


A. Alcoholism
Ethanol
Acetaldehyde
Acetic acid
H_3C
H_2COH
H_3C
HC=O
H_3C
COOH
NAD^+
NADH
NAD^+
NADH
Main catabolic pathway of ethanol in liver cell
$NADH/NAD^+$ ratio ↑
Fatty acid oxidation ↓
Fatty acid synthesis ↑
Triglyceride synthesis ↑
Fatty liver
Cell necrosis
Cirrhosis


B. Liver cirrhosis
Hepatic encepha-lopathy
Insufficient presystemic elimination of NH_3
Esophageal and gastric varices
Portal hypertension
Ascites
Liver cirrhosis

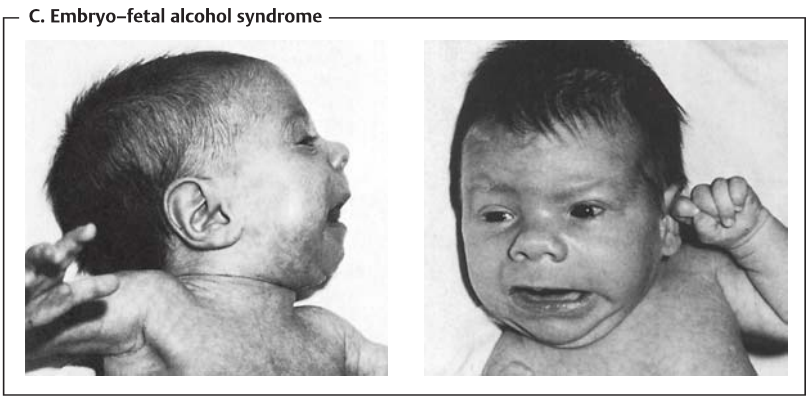

C. Embryo–fetal alcohol syndrome

Fig. 38.4

Therapy of Selected Diseases

Hypertension

Cardiovascular diseases are the leading cause of death in the Western world. Basically, atherosclerosis manifests itself in three major organs and thereby leads to severe secondary diseases. Coronary disease results from atherosclerosis of the coronary arteries and culminates in myocardial infarction when vessels are occluded by a thrombus. In the brain, atherosclerosis gives rise to arterial thrombi or ruptures that result in a stroke. Atherosclerosis in the kidney leads to renal failure. Since these diseases significantly lower life expectancy, early recognition and elimination of risk factors (hypertension, diabetes mellitus, hyperlipidemia, and smoking) that promote atherosclerosis are essential.

Hypertension is considered to be present when systolic blood pressure exceeds 140 mmHg and the diastolic value lies above 90 mmHg. Since cardiovascular risk increases over a wide range with increasing blood pressure, no "threshold value" exists that defines hypertension unequivocally. If other risk factors are present, blood pressure should be brought down to an even lower level (in diabetes mellitus below 140/85 mmHg). Therapeutic objectives comprise the prevention of organ damage and reduction of mortality. Because these target parameters cannot be measured in individual patients, the "surrogate parameter" of lowering of blood pressure is defined as the immediate goal. Before drug therapy is instituted, the patient has to be instructed to reduce body weight (BMI <30), to reduce consumption of alcohol (in men < 20–30 g ethanol/day; in women 10–20 g/day), to stop smoking, and to restrict the daily intake of NaCl (to 6 g/day).

The drugs of first choice in antihypertensive therapy are those that have been unambiguously shown in clinical studies to reduce mortality of hypertension—diuretics, ACE inhibitors, AT_1 antagonists, β-blockers, and calcium antagonists. Reducing blood pressure is important to reduce cardiovascular risk. The choice of medication is guided by concomitant diseases and possible contraindications (▶ Fig. 39.1**B**).

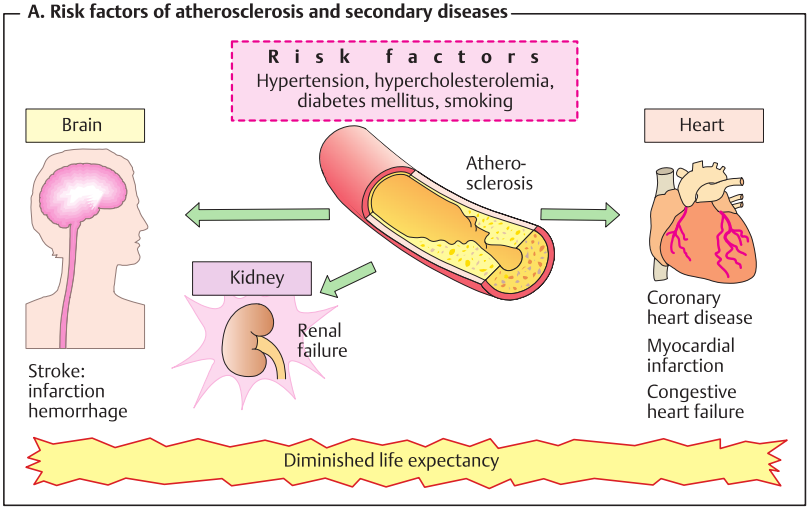
Among the diuretics, thiazides are particularly recommended for treatment of hypertension. To avoid undue loss of K^+, combination with triamterene or amiloride is often advantageous.

ACE inhibitors prevent the formation of angiotensin II by angiotensin-converting enzyme (ACE) and thereby reduce peripheral vascular resistance and blood pressure. In addition, ACE inhibitors prevent the effect of angiotensin II on protein synthesis in myocardial and vascular muscle cells, and thus diminish ventricular hypertrophy. As adverse effects, ACE inhibitors may provoke dry cough, impaired renal function, and hyperkalemia. When ACE inhibitors are poorly tolerated, an AT_1 receptor antagonist can be given.

From the group of β-adrenoceptor antagonists, **β_1-selective blockers** are mainly used (e.g., metoprolol). Owing to blockade of β_2-receptors, non-selective β-blockers can impair pulmonary function, particularly in patients with chronic obstructive lung disease.

Among **calcium antagonists,** dihydropyridines with long half-lives are advantageous because short-acting drugs, which rapidly lower blood pressure, are prone to elicit reflex tachycardia.

Fewer than 50% of hypertensive patients are adequately managed by monotherapy. If the monotherapy fails, either the drug should be discontinued or two agents should be combined in reduced dosage (thiazide and β-blocker, and/or ACE inhibitor, and/or calcium-antagonist). Combinations that abolish the counter regulation against the primary antihypertensive drug are especially effective. For instance, diuretic-induced loss of Na^+ and water leads to a compensatory activation of the renin–angiotensin system that can be eliminated by ACE inhibitors or AT_1 antagonists.


A. Risk factors of atherosclerosis and secondary diseases
Risk factors
Hypertension, hypercholesterolemia, diabetes mellitus, smoking
Brain
Heart
Athero-sclerosis
Kidney
Renal failure
Stroke: infarction hemorrhage
Coronary heart disease
Myocardial infarction
Congestive heart failure
Diminished life expectancy

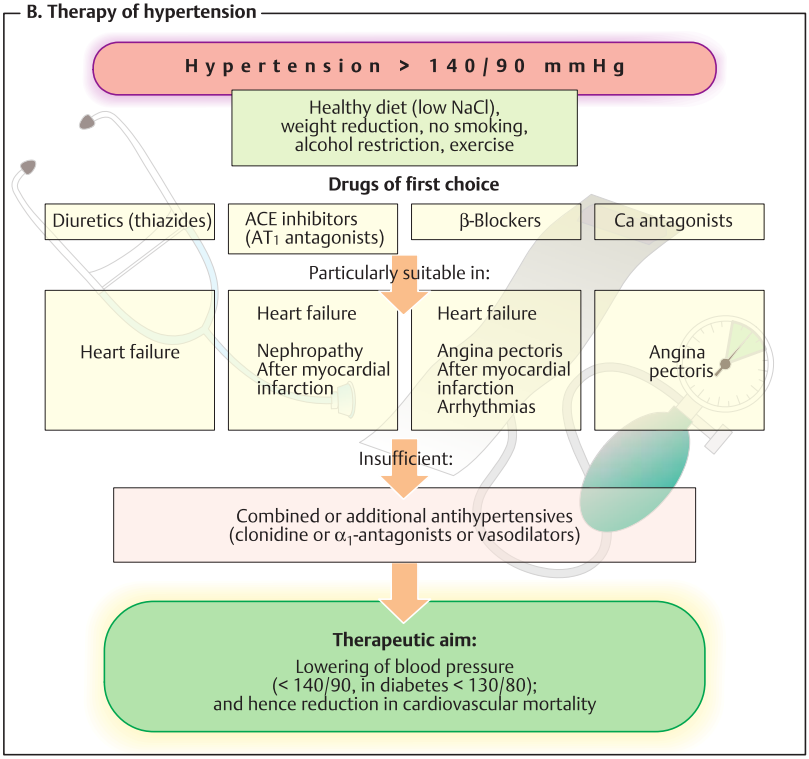

B. Therapy of hypertension
Hypertension > 140/90 mmHg
Healthy diet (low NaCl), weight reduction, no smoking, alcohol restriction, exercise
Drugs of first choice
Diuretics (thiazides)
ACE inhibitors (AT1 antagonists)
β-Blockers
Ca antagonists
Particularly suitable in:
Heart failure
Heart failure
Nephropathy
After myocardial infarction
Heart failure
Angina pectoris
After myocardial infarction
Arrhythmias
Angina pectoris
Insufficient:
Combined or additional antihypertensives (clonidine or α1-antagonists or vasodilators)
Therapeutic aim:
Lowering of blood pressure (< 140/90, in diabetes < 130/80); and hence reduction in cardiovascular mortality

Fig. 39.1

Angina Pectoris

An anginal pain attack signals transient hypoxia of the myocardium. As a rule, the *oxygen deficit* results from inadequate myocardial blood flow due to narrowing of larger coronary arteries. The underlying causes are:

- most commonly atherosclerotic change of the vascular wall *(coronary sclerosis* with exertional angina)
- very infrequently spasmodic constriction of a morphologically healthy coronary artery *(coronary spasm* with angina at rest; variant angina)
- or more often coronary spasm occurring in an atherosclerotic vascular segment.

The goal of treatment is to prevent myocardial hypoxia either by raising blood flow *(oxygen [O_2] supply)* or by lowering myocardial oxygen demand *(O_2 demand).*

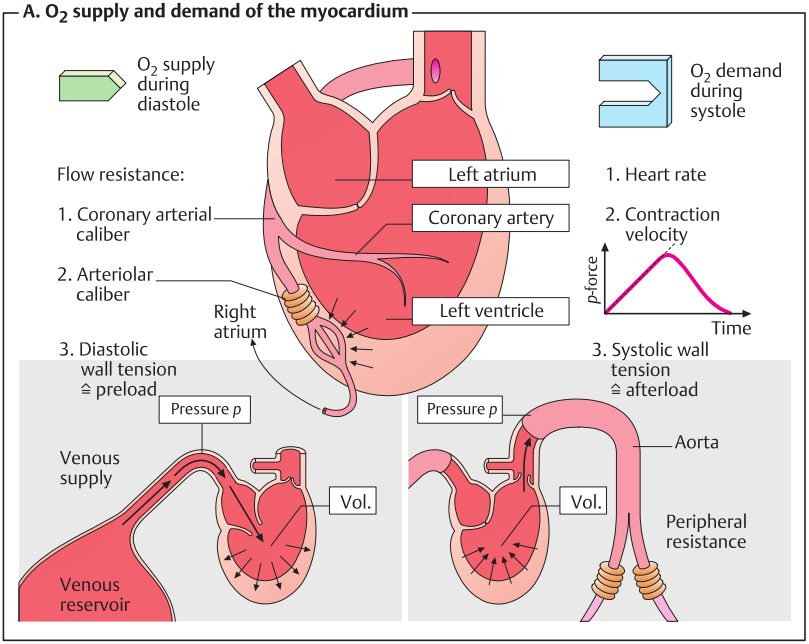
► **Factors determining oxygen supply.** The force driving myocardial blood flow is the *pressure difference* between the coronary ostia *(aortic pressure)* and the opening of the coronary sinus *(right atrial pressure).* Blood flow is opposed by *coronary flow resistance,* which includes three components:

1. Owing to their large caliber, the *proximal coronary segments* do not normally contribute significantly to flow resistance. However, in coronary sclerosis or spasm, pathological obstruction of flow occurs here. Whereas the more common coronary sclerosis cannot be overcome pharmacologically, the less common coronary spasm can be relieved by appropriate vasodilators (nitrates, nifedipine).
2. The *caliber of arteriolar resistance vessels* controls blood flow through the coronary bed. Arteriolar caliber is determined by myocardial O_2 tension and local concentrations of metabolic products, and is "automatically" adjusted to the required blood flow (► Fig. 39.2**B**, healthy subject). This *metabolic autoregulation* explains why anginal attacks in coronary sclerosis occur only during exercise (► Fig. 39.2**B**, patient). At rest, the pathologically elevated flow resistance is compensated by a corresponding decrease in arteriolar resistance, ensuring adequate myocardial perfusion. During exercise, further dilation of arterioles is impossible. As a result, there is ischemia associated with pain. Pharmacological agents that act to dilate arterioles would thus be inappropriate because at rest they may divert blood from underperfused into healthy vascular regions on account of redundant arteriolar dilation. The resulting "steal effect" could provoke an anginal attack.
3. The intramyocardial pressure, i.e., systolic squeeze, compresses the capillary bed. Myocardial blood flow is halted during systole and occurs almost entirely during diastole. *Diastolic wall tension* ("preload") depends on ventricular volume and filling pressure. The organic nitrates reduce preload by decreasing venous return to the heart.

► **Factors determining oxygen demand.** The heart muscle cell consumes the most energy to generate contractile force. O_2 demand rises with an increase in

1. *heart rate*
2. *contraction velocity*
3. *systolic wall tension* ("afterload"). The last depends on ventricular volume and the systolic pressure needed to empty the ventricle.

As peripheral resistance increases, aortic pressure rises and, hence, the resistance against which ventricular blood is ejected. O_2 demand is lowered by β-blockers and calcium antagonists, as well as by nitrates (p. 326).


A. O_2 supply and demand of the myocardium
O_2 supply during diastole
O_2 demand during systole
Flow resistance:
1. Coronary arterial caliber
2. Arteriolar caliber
3. Diastolic wall tension ≙ preload
Left atrium
Coronary artery
Left ventricle
Right atrium
1. Heart rate
2. Contraction velocity
p-force
Time
3. Systolic wall tension ≙ afterload
Pressure p
Venous supply
Vol.
Venous reservoir
Pressure p
Aorta
Vol.
Peripheral resistance

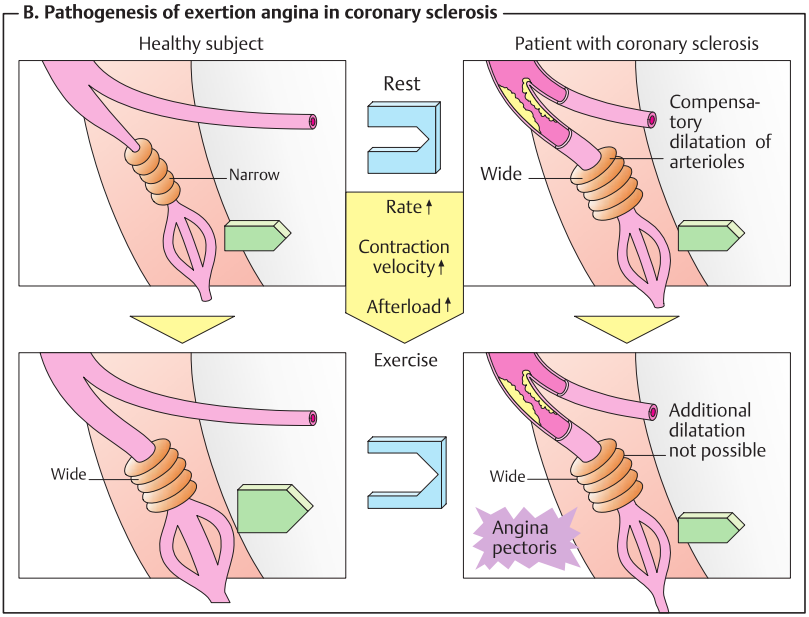

B. Pathogenesis of exertion angina in coronary sclerosis
Healthy subject
Patient with coronary sclerosis
Rest
Narrow
Wide
Compensatory dilatation of arterioles
Rate ↑
Contraction velocity ↑
Afterload ↑
Exercise
Wide
Wide
Additional dilatation not possible
Angina pectoris

Fig. 39.2

Antianginal Drugs

Antianginal agents derive from three drug groups, the pharmacological properties of which have already been presented in more detail: the organic nitrates (p. 138), the calcium antagonists (p. 140), and the β-blockers (p. 116).

Organic nitrates (▶ Fig. 39.3**A**) increase blood flow, hence O_2 supply, because diastolic wall tension (preload) declines as venous return to the heart is diminished. Thus, the nitrates enable myocardial flow resistance to be reduced even in the presence of coronary sclerosis with angina pectoris. In angina due to coronary spasm, arterial dilation overcomes the vasospasm and restores myocardial perfusion to normal. O_2 demand falls because of the ensuing decrease in the two variables that determine systolic wall tension (afterload): ventricular filling volume and aortic blood pressure.

Calcium antagonists (▶ Fig. 39.3**B**) decrease O_2 demand by lowering aortic pressure, one of the components contributing to afterload. The dihydropyridine *nifedipine,* is devoid of a cardiodepressant effect, but may give rise to reflex tachycardia and an associated increase in O_2 demand. The catamphiphilic drugs *verapamil* and *diltiazem* are cardiodepressant. Reduced beat frequency and contractility contribute to a reduction in O_2 demand; however, AV-block and mechanical insufficiency can dangerously jeopardize heart function. In coronary spasm, calcium antagonists can induce spasmolysis and improve blood flow.

β-Blockers (▶ Fig. 39.3**C**) protect the heart against the O_2-wasting effect of sympathetic drive by inhibiting β_1-receptor-mediated increases in cardiac rate and speed of contraction.

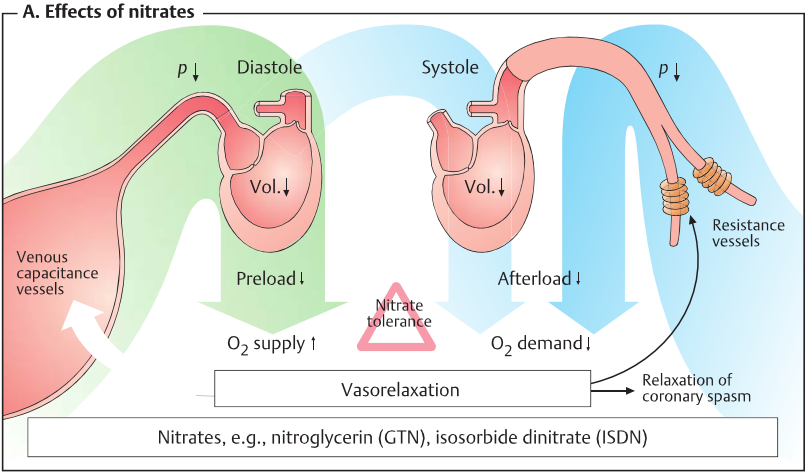
▶ **Uses of antianginal drugs.** For relief of the **acute anginal attack,** rapidly absorbed drugs are preferred (▶ Fig. 39.3**D**). The drug of choice is *glyceryl trinitrate* (GTN, nitroglycerin) 0.8–2.4 mg sublingually; onset of action within 1–2 minutes; duration of effect ~30 minutes). Isosorbide dinitrate (ISDN) can also be used (5–10 mg sublingually); compared with GTN, its action is somewhat delayed in onset but of longer duration.

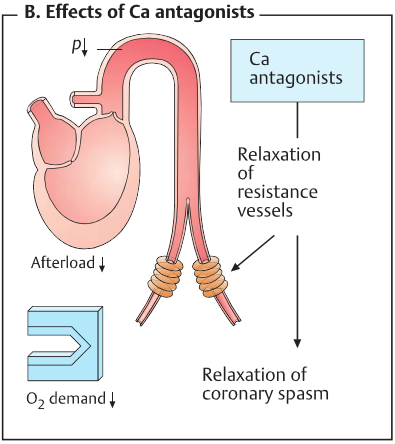
For sustained daytime **angina prophylaxis,** *nitrates* are of limited value because "nitrate pauses" of about 12 hours are appropriate if nitrate tolerance is to be avoided. If attacks occur during the day, ISDN or its metabolite *isosorbide mononitrate* may be given in the morning and at noon (e.g., ISDN 40 mg in extended-release capsules). Because of hepatic presystemic elimination, GTN is not suitable for oral administration. Continuous delivery via a transdermal patch would also not seem advisable because of the potential development of tolerance. With *molsidomine,* there is less risk of nitrate tolerance; however, its clinical use is restricted owing to its potential carcinogenicity.

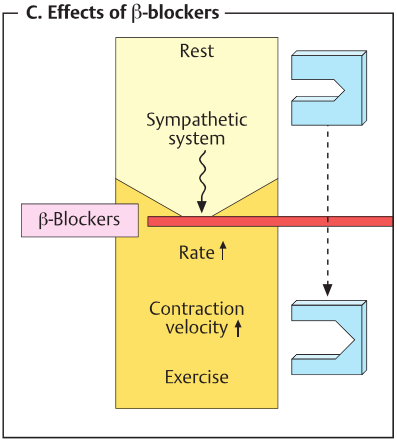
When choosing a calcium antagonist it must be ensured that long-acting substances (e.g., *amlodipine, nicardipine)* or a sustained-release formulation of short-acting substances *(nifedipine retard)* are prescribed in order to avoid reflex tachycardia. When *β-blockers* are given, the potential consequences of reducing cardiac contractility (withdrawal of sympathetic drive) must be kept in mind. Since vasodilating β_2-receptors are blocked, an increased risk of vasospasm cannot be ruled out. Therefore, monotherapy with β-blockers is recommended only in angina due to coronary sclerosis, but not in variant angina. If β-blockers are contraindicated, *ivabradine* may be used. This reduces the heart rate at rest and during exercise by blocking cardiac pacemaker channels.

Ranolazine, which inhibits late Na^+ influx, thereby improving cardiomyocyte energy balance, is another reserve drug.

To improve the long-term prognosis of coronary heart disease, the following drugs are used in addition: low-dose acetylsalicylic acid, statins (if LDL-cholesterol is raised), ACE inhibitors, and β-blockers if heart failure or myocardial infarction is also present.


A. Effects of nitrates
p↓
Diastole
Vol.↓
Venous capacitance vessels
Preload↓
O2 supply↑
Systole
Vol.↓
p↓
Resistance vessels
Afterload↓
O2 demand↓
Nitrate tolerance
Vasorelaxation
Relaxation of coronary spasm
Nitrates, e.g., nitroglycerin (GTN), isosorbide dinitrate (ISDN)


B. Effects of Ca antagonists
p↓
Ca antagonists
Relaxation of resistance vessels
Afterload↓
O2 demand↓
Relaxation of coronary spasm


C. Effects of β-blockers
Rest
Sympathetic system
β-Blockers
Rate↑
Contraction velocity↑
Exercise

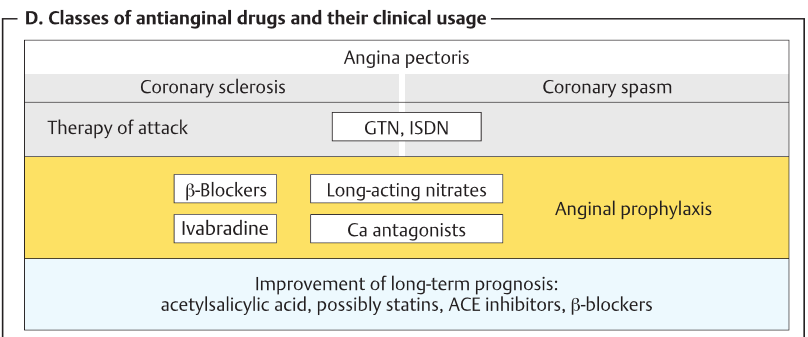

D. Classes of antianginal drugs and their clinical usage
Angina pectoris
Coronary sclerosis
Coronary spasm
Therapy of attack
GTN, ISDN
β-Blockers
Long-acting nitrates
Ivabradine
Ca antagonists
Anginal prophylaxis
Improvement of long-term prognosis:
acetylsalicylic acid, possibly statins, ACE inhibitors, β-blockers

Fig. 39.3

Acute Coronary Syndrome—Myocardial Infarction

Myocardial infarction (MI) is caused by the occlusion of a coronary artery or one of its branches. The myocardial region that has been cut off from its blood supply dies within a short time owing to the lack of O_2 and glucose. In the area bordering the infarct, the oxygen supply to cardiac muscle cells is reduced and the membrane potential becomes unstable. Spontaneous pacemaker potentials may develop, leading to fatal ventricular fibrillation. The loss of functional muscle tissue results in reduced cardiac performance. The falling blood pressure stimulates the sympathetic system: the heart rate is increased via β-receptors and peripheral resistance is increased via α-receptors, so the heart's oxygen demand rises. This results in further worsening of the cardiac situation. The patient experiences severe pain, a feeling of annihilation, and fear of dying.

MI usually develops after rupture or erosion of an atherosclerotic plaque (▶ Fig. 39.4**A**). At this site, platelets and the clotting system are activated and a thrombus can form rapidly, further narrowing the lumen. Regardless of subsequent therapeutic measures, **immediate therapy** must be initiated by the emergency physician in all patients with suspected MI. To relieve the patient from severe pain and anxiety, morphine and a benzodiazepine (diazepam) need to be given. Antiplatelet drugs and heparin as anticoagulant are necessary for preventing further formation of thrombi. GTN can be used to reduce cardiac load. When blood pressure and heart rate have stabilized, a β-blocker can be administered to lower cardiac O_2 consumption and the risk of arrhythmias. Infusion of lidocaine is required to counter the threat of arrhythmias. After the initial measures, the patient must be transported to hospital as quickly as possible. The chance of survival of the MI patient depends on the interval between the onset of infarction and the start of therapy.

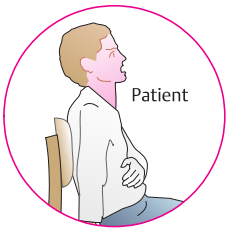
The ECG and laboratory tests determine the diagnosis and further therapy. ST segment elevation is evidence of occlusion of a large coronary artery ("STEMI"). In this case, rapid reperfusion is often life-saving. If the patient has been brought to a cardiac center, cardiac catheterization with balloon dilation of the stenosis is usually performed. The risk of coronary artery restenosis at this site can be reduced by insertion of a stent. Both bare metal stents and coated stents are employed. The surface of a stent can have a medicated coating that slowly releases paclitaxel or sirolimus. These drugs are intended to diminish neointima formation and hence the danger of restenosis. Following stent insertion, antiplatelet treatment with acetylsalicylic acid and an ADP ($P2Y_{12}$) receptor antagonist such as clopidogrel is recommended.

If cardiac catheterization is not available, intravenous fibrinolysis to dissolve the thrombus can be instituted within the first 12 hours after the start of the infarct symptoms.

If the patient has acute coronary syndrome without ST elevation ("NSTEMI") or unstable angina pectoris, pharmacological therapy is begun (▶ Fig. 39.4**A**) and cardiac catheterization is performed to look for coronary stenosis. Because of the risk of bleeding, fibrinolytic drugs are contraindicated in NSTEMI or unstable angina pectoris.

Post-MI management calls for strict adherence to a program of secondary prevention. The patient must reduce cardiac risk factors and implement cessation of smoking, optimal control of diabetes mellitus, and physical exercise (a dog that loves to run is an ideal training partner). Supportive pharmacotherapeutic measures include administration of platelet aggregation inhibitors, β-blockers, statins, and ACE inhibitors.

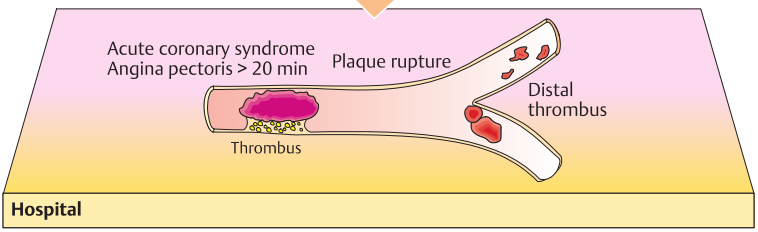
A. Myocardial infarction: pharmacotherapeutic approaches



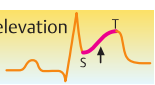
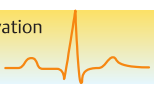
Acute symptoms:
severe pain,
sense of impending doom,
fear of dying

Acute care measures:
- Nitroglycerin (reduction of pre- and afterload)
- Acetylsalicylic acid (if needed i.v.) (inhibition of platelet aggregation)
- Morphine (analgesia, sedation)
- Oxygen via nasal tube

Hospitalization with minimal delay



Hospital

ECG	ST-elevation 	No ST-elevation 	
Laboratory	CK-MB ↑ Troponin-I, -T ↑	Troponin-I, -T ↑	–
Diagnosis	Myocardial infarction ("STEMI")	Myocardial infarction ("NSTEMI")	Unstable angina pectoris
Initial therapy	Acetylsalicylic acid, heparin, nitrates, β-blockers		

Restoration of perfusion

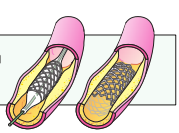
Cardiac catheterization

Fibrinolysis

GPIIb/IIIa antagonists

Surgery

Balloon dilatation + stent



Stent coating: paclitaxel, sirolimus

Inhibition of cell proliferation

Secondary prevention

Discharge:

- acetylsalicylic acid
- β-blocker
- ACE inhibitor

possibly:
- clopidogrel
- phenprocoumon
- statins

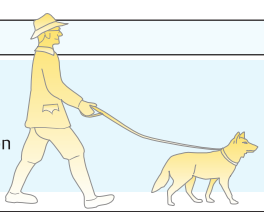


Fig. 39.4

Congestive Heart Failure

In chronic congestive heart failure, cardiac pump performance falls below a level required by the body's organs for maintaining function and metabolism (▶ Fig. 39.5**A**). The most common primary causes of heart failure are coronary disease, hypertension, volume overload, or cardiomyopathies. Diminished cardiac performance leads to precardial congestion of venous blood. Congestion in front of the left ventricle causes dyspnea and pulmonary edema. Ankle edema, enlarged liver, and ascites signal congestion in front of the right ventricle.

The degree of severity of myocardial failure is categorized according to the New York Heart Association (NYHA) Functional Classification System (▶ Fig. 39.5**B**). Stages I–IV reflect an increasing level of disability.

The decrease in cardiac function activates several **compensatory mechanisms** that operate to maintain perfusion of organs (▶ Fig. 39.5**A**). These include activation of the sympathetic nervous system and of the renin–angiotensin system. Increased release of norepinephrine raises cardiac rate and evokes peripheral vasoconstriction. Increased production of angiotensin II promotes both vasoconstriction and release of aldosterone from the adrenals. These compensations increase cardiac afterload and plasma volume is expanded because the kidney retains water and sodium. Although such "auxiliary" countermeasures afford transient help in maintaining cardiac output, (nor)epinephrine, aldosterone, and angiotensin II promote the progression of myocardial insufficiency. Successful therapy of chronic congestive failure is therefore contingent on **inhibition of compensation mechanisms.**

β-Blockers are used successfully in the management of heart failure (▶ Fig. 39.5**B**). Every 2–3 weeks, the daily dose can be increased in small increments, as long as the patient does not develop bradycardia.

ACE inhibitors are the appropriate agents for inhibiting the **renin–angiotensin II system.** The effect of angiotensin II receptor antagonists is equivalent to that of ACE inhibitors. Both interventions for attenuating compensatory mechanisms improve the clinical state of patients (less hospitalization) and increase life expectancy.

Diuretics are essential in the treatment of edema, dyspnea, and advanced congestive failure.

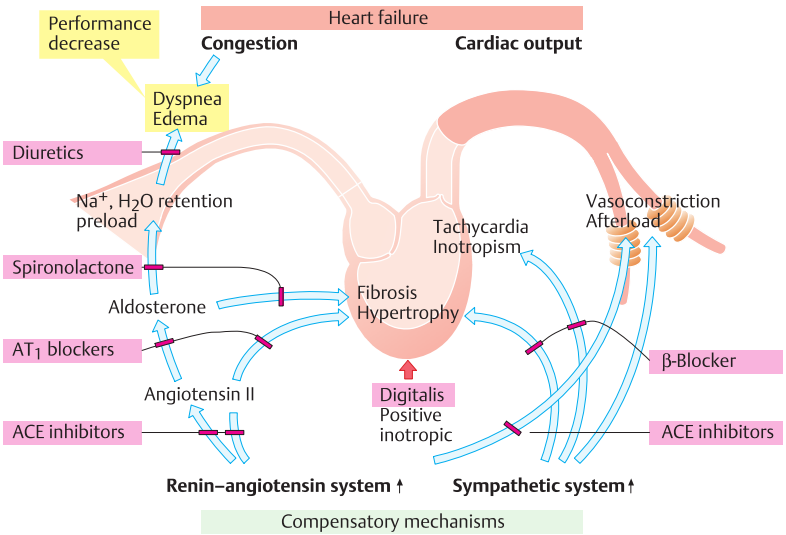
Treatment with an aldosterone antagonist is indicated when the action of aldosterone is enhanced as physiological compensation for congestive cardiac failure. **Spironolactone** is the classic antagonist, though it does not have highly specific affinity for aldosterone receptors but also binds to sex hormone receptors. **Eplerenone** is a newer drug that is a very specific aldosterone receptor antagonist so this should be given precedence. Block of cardiac mineralocorticoid receptors is intended to reduce the chronic interstitial fibrosis associated with congestive heart failure. Hyperkalemia may be a side effect, so the serum potassium level should be monitored.

If the heart rate remains above 70 beats/min despite β-receptor blockade, ivabradine can be given to reduce the tachycardia and improve symptoms.

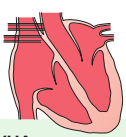
Digitalis glycosides augment the contractile force of cardiac muscle and are indicated in severe chronic heart failure, especially in the presence of concomitant atrial fibrillation. Successful digitalization can be confirmed by diuresis (monitor the patient's weight), improvement in dyspnea, and slowing of the heart rate. Digoxin is the preferred digitalis preparation because of its favorable pharmacokinetics. Digitoxin's long $t_{1/2}$ (about 7 days) is highly impractical. Acetyl- and methyldigoxin have no advantages compared with digoxin. Digitalis glycosides improve the patient's clinical situation but have not been shown to improve mortality.

Drugs with an acute positive inotropic action (e.g., catecholamines or phosphodiesterase inhibitors) may be of transient help in sudden decompensation but must not be given in chronic congestive failure.

A. Congestive heart failure



B. Classification and drug therapy of congestive heart failure



Impairment of cardiac function

NYHA Functional Class	I	II	III	IV
Clinical symptoms	—	Slight	Marked	At rest
ACE inhibitors	+	+	+	+
AT_1 blocker	when ACE inhibitors cause adverse effects, e.g., cough			
β-Blocker	Infarction Hypertension	+	+	+
Diuretics	Hypertension Edema	+	+	+
Aldosterone antagonists	—	Hypokalemia	+	+
Digitalis	Atrial fibrillation	Atrial fibrillation	+	+

Fig. 39.5

Septic Shock

A distinction is made between cardiogenic shock, hypovolemic shock, and septic shock (▶ Fig. 39.6**A**). It is easy to understand how cardiogenic shock is caused by inadequate cardiac pump function and hypovolemic shock by massive blood or plasma loss. Septic shock, on the other hand, is based on a complicated cascade of reactions triggered by molecules on the surface of bacteria and fungi. This section deals only with septic shock and its management.

The processes that take place during sepsis are extremely varied. It is triggered by microorganisms that are either pathogenic from the start or become pathogenic by "migrating" from one body compartment to another. Substances such as lipopolysaccharide or mureins are present on the cell surface of bacteria and fungi; mureins are found particularly on Gram-positive bacteria. These substances bind to toll-like receptors (TLR) located on cells of the immune system. Binding activates cytosol nuclear factor (NF-κB), which stimulates cytokine transcription in the cell nucleus. Interleukins such as tumor necrosis factor α (TNFα) and interleukin-1β are then released and produce inflammation. Directly or indirectly by releasing further "active substances," these worsen the symptoms of septic shock, which may terminate in **multiorgan failure.**

Induction of COX-2, leading to increased prostaglandin production, is another mechanism that plays a negative part in sepsis. These arachidonic acid derivatives promote inflammatory reactions, reduce the pain threshold, and cause fever.

It is not possible to predict which of these mechanisms will be involved in an individual case and determine the course of the disease. Determining factors include the severity of the primary infection, the patient's physical condition, the pathogens responsible for the sepsis, how many organs are involved, and how quickly and consistently therapy is instituted and provided.

The treatment of septic shock (▶ Fig. 39.6**B**) can be divided into **immediately needed measures** and procedures to deal with the disease and the patient's individual course. The first priority is to **remove the focus of infection** and start **anti-infectious therapy.** Removal of the infection focus often requires surgery. An antibiotic or antibacterial drug must be started immediately even before identifying the type of organism and determining its sensitivity. A drug with the broadest possible spectrum must be given in high dosage. A specific drug can be used following bacterial diagnosis.

Just as urgent is treatment of hypotension, which leads to underperfusion and impaired function of many organs such as the heart, lungs, kidneys, and brain. Use of vasoconstrictor drugs is often necessary in addition to volume replacement with electrolyte solutions in order to achieve adequate blood pressure. This is called **controlled-volume catecholamine therapy.** Thrombosis prophylaxis should also be given.

Other measures such as artificial ventilation may be necessary depending on the case. If the kidneys stop functioning, dialysis must be employed. Pyrexia can be reduced by antipyretics (acetaminophen) and severe pain by analgesics. Use of central depressant drugs is inadvisable. It is worth noting that administration of corticosteroids has hardly any positive effect in septic shock.

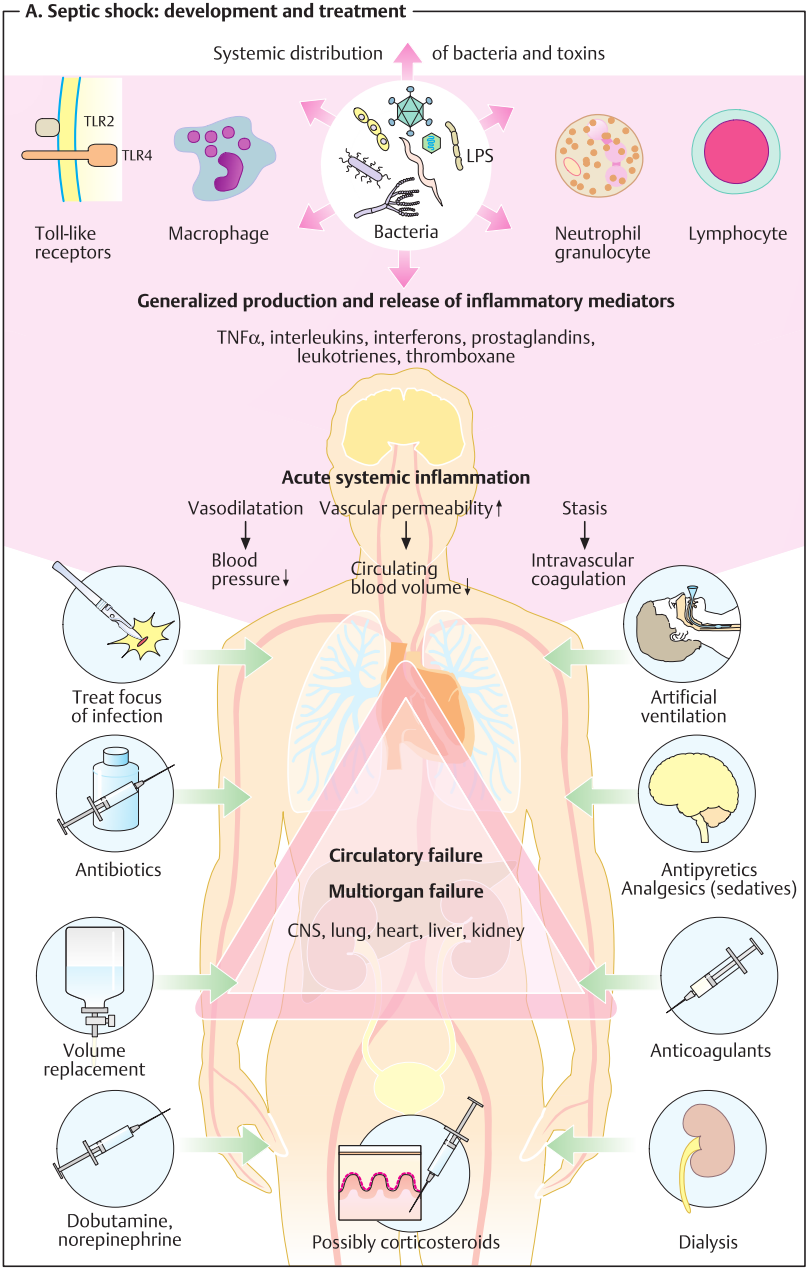

A. Septic shock: development and treatment
Systemic distribution of bacteria and toxins
TLR2
TLR4
LPS
Toll-like receptors
Macrophage
Bacteria
Neutrophil granulocyte
Lymphocyte
Generalized production and release of inflammatory mediators
TNFα, interleukins, interferons, prostaglandins, leukotrienes, thromboxane
Acute systemic inflammation
Vasodilatation
Vascular permeability↑
Stasis
Blood pressure↓
Circulating blood volume↓
Intravascular coagulation
Treat focus of infection
Artificial ventilation
Antibiotics
Antipyretics
Analgesics (sedatives)
Circulatory failure
Multiorgan failure
CNS, lung, heart, liver, kidney
Volume replacement
Anticoagulants
Dobutamine, norepinephrine
Possibly corticosteroids
Dialysis

Fig. 39.6

Antiparkinsonian Drugs

In order to carry out purposive movement, impulses pass from the motor cortex via the spinal cord to the appropriate muscles. At the same time, the movement pattern is coordinated by impulses that pass through various parts of the brain and send messages back to the motor cortex. One of these motor circuits passes through the cerebellum and another through the basal ganglia. A disorder localized in the basal ganglia is known as **Parkinson disease** (shaking palsy). The disease typically manifests at an advanced age and is characterized by tremor at rest, muscle stiffness (rigidity), poverty of movement (akinesia), and increasing impairment in quality of life.

The primary disorder is degeneration of dopaminergic ganglion cells in the substantia nigra; these project as the nigrostriatal tract to the corpus striatum (putamen and caudate nucleus), where they exert an inhibitory effect. Excitatory cholinergic neurons also terminate in the striatum.

Pharmacotherapeutic measures are aimed at compensating dopamine deficiency or suppressing unopposed cholinergic activity.

► **L-Dopa.** Dopamine itself cannot penetrate the blood–brain barrier; however, its natural precursor, L-**d**ihydr**o**xy**p**henyl**a**lanine (levodopa), is effective in replenishing striatal dopamine levels, because it is transported across the blood–brain barrier via an amino acid carrier and is subsequently decarboxylated by dopa decarboxylase, present in striatal tissue. Decarboxylation also takes place in peripheral organs where dopamine is not needed and is likely to cause undesirable effects (vomiting; hypotension). Extracerebral production of dopamine can be prevented by inhibitors of dopa decarboxylase (carbidopa, benserazide) that do not penetrate the blood–brain barrier, leaving intracerebral decarboxylation unaffected.

Excessive elevation of brain dopamine levels may lead to undesirable reactions such as involuntary movements (dyskinesias) and mental disturbances.

► **Dopamine receptor agonists.** CNS dopamine deficiency can be compensated by lysergic acid derivatives such as *bromocriptine* (p. 128), *lisuride, pergolide,* and *cabergoline.* These derivatives can damage heart valve morphology, impairing valve function. Other dopamine agonists that are not derived from lysergic acid are pramipexole, ropinirole, and rotigotine. The latter is used transdermally.

► **Monoamine oxidase-B (MAO-B) inhibitors.** MAO-B can be inhibited by *selegiline* or *rasagiline.* Degradation of biogenic amines in peripheral organs is not affected because MAO-A remains functional.

► **Inhibitor of catechol O-methyltransferase (COMT).** The CNS-impermeant entacapone inhibits peripheral degradation of L-dopa and thus enhances availability of L-dopa for the brain. Tolcapone is a reserve drug that penetrates the CNS.

► **Anticholinergics.** Centrally acting muscarinic receptor antagonists (p. 128), such as *biperiden,* can be used to suppress the relative predominance of cholinergic activity, particularly tremor. They are little used now because the typical atropine-like side effects limit the tolerable dose.

► **Amantadine.** Early or mild parkinsonian manifestations may be relieved temporarily by amantadine. The underlying mechanisms of action may involve blockade of ligand-gated ion channels of the glutamate/NMDA subtype, ultimately leading to diminished release of acetylcholine.

Treatment of advanced Parkinson disease requires combined administration of the above drugs for ameliorating the symptoms of this grave condition. Commonly, additional signs of central degeneration develop as the disease progresses.

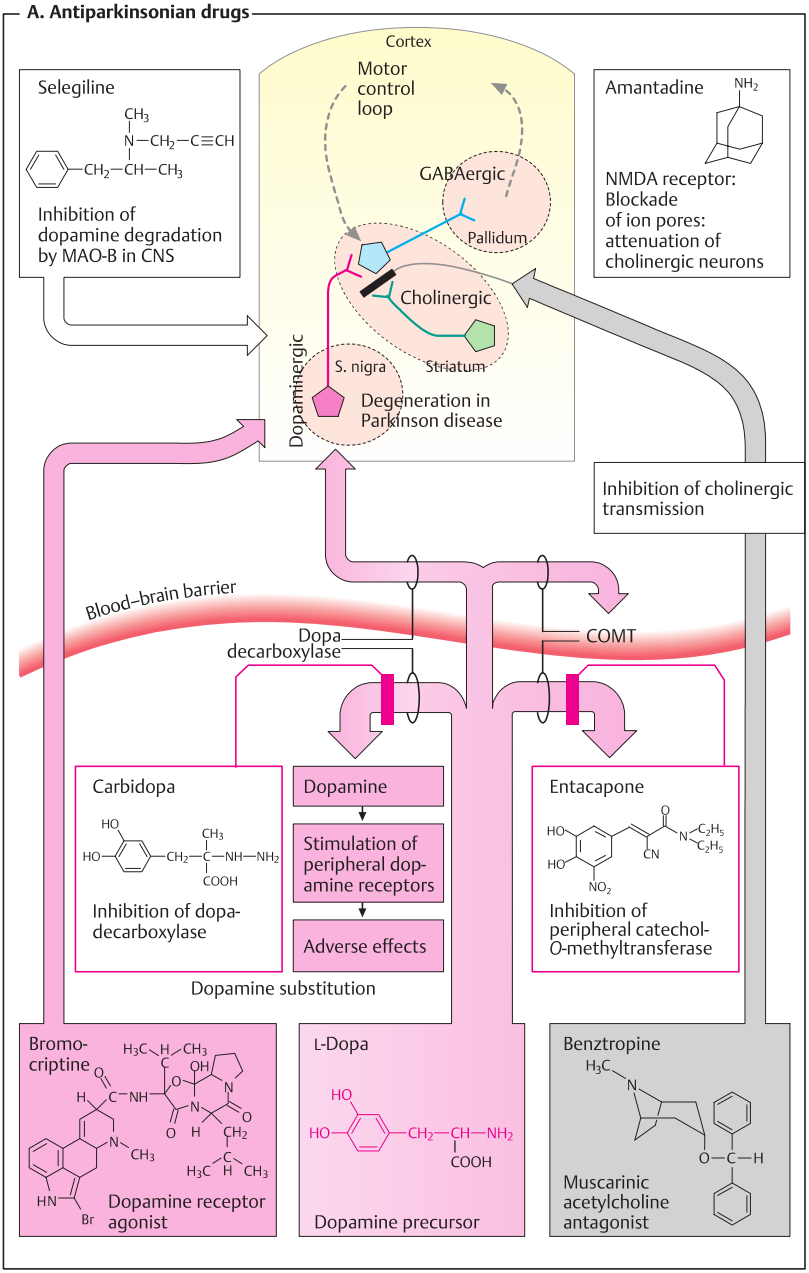

A. Antiparkinsonian drugs
Cortex
Motor control loop
Selegiline
Inhibition of dopamine degradation by MAO-B in CNS
Amantadine
NMDA receptor: Blockade of ion pores: attenuation of cholinergic neurons
GABAergic
Pallidum
Cholinergic
Striatum
S. nigra
Dopaminergic
Degeneration in Parkinson disease
Inhibition of cholinergic transmission
Blood–brain barrier
Dopa-decarboxylase
COMT
Carbidopa
Inhibition of dopa-decarboxylase
Dopamine
Stimulation of peripheral dopamine receptors
Adverse effects
Dopamine substitution
Entacapone
Inhibition of peripheral catechol-O-methyltransferase
Bromo-criptine
Dopamine receptor agonist
L-Dopa
Dopamine precursor
Benztropine
Muscarinic acetylcholine antagonist

Fig. 40.1

Antiepileptic Drugs

Epilepsy is a *chronic* brain disease of diverse etiology; it is characterized by *recurrent paroxysmal* episodes of uncontrolled excitation of brain neurons. The term epilepsy therefore refers not to the seizure but to the underlying brain dysfunction. Involving larger or smaller parts of the brain (▶ Fig. 40.2**A**), the electrical discharge is evident in the electroencephalogram (EEG) as synchronized rhythmic activity and manifests itself in motor, sensory, psychic, and vegetative (visceral) phenomena. As both the affected brain region and the cause of abnormal excitability may differ, epileptic seizures can take on many forms. From a pharmacotherapeutic viewpoint, the classification may be:

- Phenomenological according to seizure type (focal or generalized)
- Etiological according to seizure cause: symptomatic/structural (approximately 85% of cases) or idiopathic/genetic (approximately 15%).

Symptomatic seizures are typically focal but can become generalized (grand mal). Idiopathic seizures are generalized from the outset (e.g., absences, myoclonic and impulsive seizures, grand mal).

Seizures are diagnosed and classified on the basis of (third-party) history, home video recording, electroencephalography (EEG), cerebral imaging (MRI) etc.

It is hardly ever possible to cure epilepsy because research into the underlying structural and functional disturbances is far from complete. The aim of treatment is to prevent seizures and this must usually be lifelong, unless the cause of the epilepsy has ceased.

The brief duration of a single epileptic fit makes acute drug treatment infeasible. Only in the case of *status epilepticus* (succession of several tonic-clonic seizures) is acute anticonvulsant therapy indicated—usually with benzodiazepines given i.v. or, if needed, buccally, nasally, or rectally.

The initiation of an epileptic attack involves "pacemaker" cells; these differ from other nerve cells by their unstable resting membrane potential; i.e., a depolarizing membrane current persists after the action potential terminates.

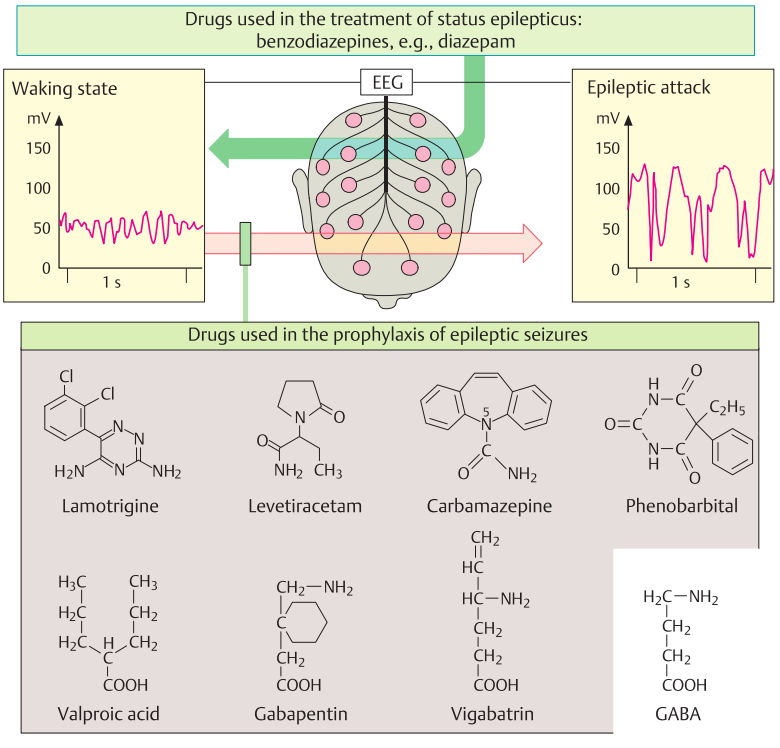
Therapeutic interventions aim to stabilize neuronal resting membrane potential and, hence, to lower excitability. In specific forms of epilepsy, an attempt is made to achieve control of seizures. *Lamotrigine and levetiracetam* are usually the drugs of first choice for long-term treatment of *focal epilepsy, with valproate used for generalized epilepsy.* Antiepileptic drugs with enzyme-inducing and enzyme-inhibiting side effects should be avoided as far as possible. This not only protects against pharmacokinetic interactions between the anticonvulsants but also avoids potential problems whenever other medicines have to be taken for a different indication. The dosage is increased until seizures are no longer present or adverse effects become unacceptable. Only when monotherapy with different agents proves inadequate can change-over to a second-line drug or combined use ("add on") be recommended (▶ Fig. 40.2**B**), provided that the possible risk of pharmacokinetic interactions is taken into account (see below).

In principle, responsivity can be decreased by inhibiting excitatory or activating inhibitory neurons. The transmitters utilized by most excitatory and inhibitory neurons are glutamate and γ-aminobutyric acid (GABA), respectively.

Glutamate (excitatory) receptors comprise three subtypes, of which the *NMDA subtype* has the greatest therapeutic importance. (*N*-methyl-D-aspartate is a synthetic selective agonist.) This receptor is a ligand-gated ion channel that, upon stimulation with glutamate, permits entry of both Na^+ and Ca^{2+} into the cell. A chloride ion channel is important for GABA (inhibitory) and its function can be increased through an allosteric binding site.

Benzodiazepines augment the activation of the $GABA_A$ receptor by physiologically released amounts of GABA via the allosteric pathway (see also p. 222). Chloride influx is increased, counteracting depolarization. *Tiagabine* blocks removal of GABA from the synaptic cleft by decreasing its reuptake. *Vigabatrin* inhibits enzymatic GABA catabolism (▶ Fig. 40.2**B**).

A. Epileptic seizure, EEG, and antiepileptic drugs



B. Indications for antiepileptics

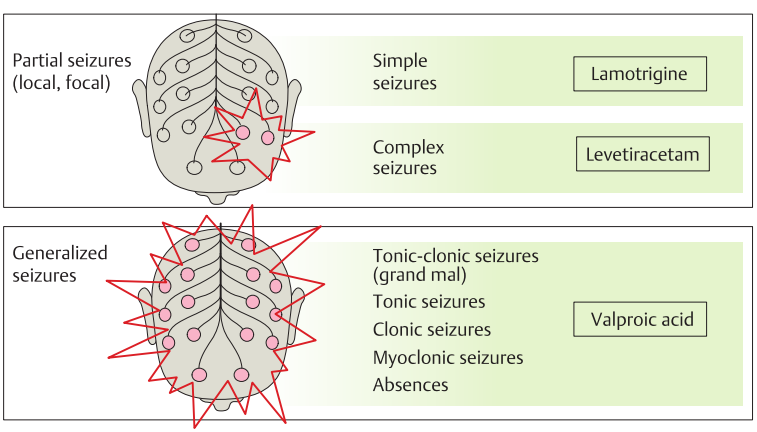


Fig. 40.2

▶ Fig. 40.3 summarizes the information provided by the manufacturers regarding the more frequent mechanisms of anticonvulsant action of their drugs:

- Blockade of depolarizing excitatory ion channels: Na^+, Ca^{2+}
- Opening of repolarizing inhibitory K^+ channels
- Inhibition of activating receptors, e.g., glutamate receptors
- Activation of inactivating receptors, e.g., GABA receptors.

In most cases, the *molecular mechanism of action of antiepileptic drugs* is not known precisely. This is hardly surprising in view of the currently little-understood complexity of cerebral function. In seeking the molecular mechanism of action the experimental pharmacologist is obliged to simplify complex systems, but this departs from the real situation. For instance, to measure the effect of a test substance on a certain type of ion channel, the electrophysiologist may have to disable other ion channels that could interfere. Binding of substances to potential target structures can be measured in membrane suspensions of genetically modified cells (e.g., Chinese hamster ovarian cells) transfected with the gene for the desired target structure. However, measurement in membrane homogenates means that the physiological potential difference between the inside and outside of a cell membrane is abolished. For these reasons, it is possible that a molecular mechanism of action observed in the laboratory plays hardly any part in the complex therapeutic effect.

Knowledge of a molecular mechanism of action meets the pragmatic human need for causality but is of secondary importance when it comes to the clinical usefulness of a medicine, where evidence of efficacy (e.g., a statistically significant fall in seizure frequency), tolerability (few adverse effects), and benefit (significant improvement in the patient's quality of life) are what count.

All antiepileptic drugs are likely, albeit in different degrees, to produce **adverse effects.** *Sedation, difficulty concentrating,* and *slowing of psychomotor drive* encumber practically all antiepileptic therapy. Moreover, cutaneous, hematological, and hepatic changes may necessitate a change in medication. Phenobarbital, primidone, and phenytoin may lead to *osteomalacia* (vitamin D prophylaxis) or *megaloblastic anemia* (folate prophylaxis). During treatment with phenytoin, *gingival hyperplasia* may develop in ~20% of patients.

Carbamazepine exerts an antidiuretic effect (sensitization of collecting ducts to vasopressin). It is also used to treat trigeminal neuralgia and neuropathic pain.

Valproate, carbamazepine, and other anticonvulsants pose teratogenic risks. Despite this, treatment should continue during *pregnancy,* as the potential threat to the fetus by a maternal seizure is greater. However, it is mandatory to use the lowest dose affording safe and effective prophylaxis. Concurrent high-dose administration of folate may prevent neural tube defects.

Carbamazepine, phenytoin, phenobarbital, and other anticonvulsants induce hepatic enzymes responsible for drug biotransformation; valproate is a potent inhibitor. *Combinations between anticonvulsants* or with other drugs may result in **clinically important interactions** (plasma level monitoring!).

When **seizures** occur in **children,** it is necessary to establish whether these are due to epilepsy or are febrile convulsions, which are associated with a rise in temperature or high fever. In this case, antiepileptic drugs are not indicated but rather antipyretic measures. However, if the child has a genuine epileptic seizure disorder, consistent treatment with antiepileptic drugs to achieve freedom from seizures is desirable. This can be difficult. Childhood epilepsies may resolve spontaneously. This positive development should not be missed because of uncritical long-term antiepileptic treatment.

Certain drugs (neuroleptics, isoniazid and high-dose β-lactam antibiotics) are able to lower the **seizure threshold** and are therefore contraindicated in epileptic patients.

Benzodiazepines are less suitable for long-term treatment because of tolerance, but they are the treatment of choice in *status epilepticus* (see above).

A. Possible sites of action of antiepileptic drugs (according to the manufacturers' information as of May 2014)

Carbamazepine, e.g., Tegretol® "**... inhibits synaptic transmission,** thereby reducing the transmission of convulsive discharges ..."

Phenobarbital, Luminal® "... doses that ... prevent convulsions in mice are below the generally sedating doses ..."

Eslicarbazepine, Zebinix® "...precise mechanism of action ... not known ... inactive state of voltage-gated **sodium channels** stabilized ..."

Phenytoin, Epanutin® "... has a **hyperpolarizing effect** on excitable membranes and is thought to act by increasing inhibitory impulse activity ..."

Lamotrigine, Lamictal® "... indicate that ... is an action- and voltage-dependent blocker of voltage-gated **sodium channels** ... inhibits ... neuronal discharge and release of glutamate ..."

Lacosamide, Vimpat® "... precise mechanism of action has yet to be explained in full ... slow inactivation of voltage-gated **sodium channels** increased selectively ..."

Zonisamide, Zonegran® "... appears ... to act ... on voltage-gated **sodium and calcium channels** ... in addition ... modulatory effect on **GABA**-mediated neuronal inhibition ..."

Rufinamide, Inovelon® "... modulates the activity of **sodium channels** and prolongs their inactivated state ..."

Gabapentin, Neurontin® "... mechanism of action unknown ... as binding site ... alpha-2-delta subunits of voltage-gated **calcium channels** identified ..."

Levetiracetam, e.g., Keppra® "... Ca^{2+} flux mediated by N-type channels **partially inhibited, release of Ca^{2+}** from intraneuronal stores diminished ... **synaptic vesicle proteins 2A** ..."

Retigabine, Trobalt® "... **calcium channels** in neurons opened (KCNQ2 ... and KCNQ3 ...). Resting membrane potential stabilized ... Several hereditary human diseases are due to mutations of the KCNQ channels, including epilepsy (KCNQ2 and 3) ... other mechanisms ... still to be fully researched ..."

Pregabalin, Lyrica® "... binds to an auxiliary subunit (alpha-2-delta protein) of voltage-gated **calcium channels** in the CNS ..."

Clonazepam, e.g., Rivotril® "... like other benzodiazepines ... anticonvulsant effect ... stronger than the other active qualities ... **increase ... GABA** ..."

Valproic acid, e.g., Epilim® "... increase in **GABA-mediated inhibition by** ... presynaptic effect on ... GABA metabolism and/or ... direct postsynaptic **effect on the ion channels of the neuron membrane ...**"

Tiagabine, Gabitril® "... potent and selective inhibitor ... GABA uptake ... in nerves and glial cells inhibited. Rise in the **GABA** concentration in the brain ..."

Stiripentol, Diacomit® "...appears ... to increase **GABA** ... duration of opening ... of the GABA-A receptor chloride ion channels increased by a barbiturate-like mechanism ..."

Ethosuximide, e.g., Zarontin® "... mechanism of action ... largely unexplained; an inhibitory effect on **GABA** breakdown was found ..."

Vigabatrin, *Sabril®* "... increases the **GABA** concentration ... selective irreversible inhibitor of GABA transaminase ..."

Perampanel, Fycompa® "... first representative of the drug class of selective, noncompetitive antagonists of the ionotropic **AMPA (...) glutamate receptor** ..."

Felbamate, e.g., Felbatol® "...The precise mechanism of action is not yet known ... no ... inhibitory effect on GABA ... receptor binding ... not an NMDA antagonist ..."

Fig. 40.3

Treatment of Migraine

► **Symptoms.** About one person in ten in Western Europe and the USA is affected by this severe, episodic form of headache. Women suffer from it twice as often as men. It is accompanied by typical symptoms, nearly always nausea and vomiting, and often sensory oversensitivity (► Fig. 40.4**A**). Migraine attacks last 24 hours on average (range 4–72 hours) and recur monthly or more often. The attack may be preceded by an aura in about one-third of cases, often in the form of visual disturbances such as fortification spectra. There may also be dysarthria. The aura lasts barely an hour and disappears before the onset of the headache. Rarely, there are cases of aura without headache. A migraine attack can be provoked by menstruation, changes in sleep/waking pattern, psychological stress or its relief, and consumption of alcohol, especially red wine.

► **Pathophysiology.** The headache originates in meningeal blood vessels (► Fig. 40.4**B**). The brain itself is not sensitive to pain. The pain is due to arterial and arteriolar dilatation, which is associated with a local aseptic inflammatory reaction. This is triggered by messengers that are released (unnecessarily) by nerve fibers to the vessels.

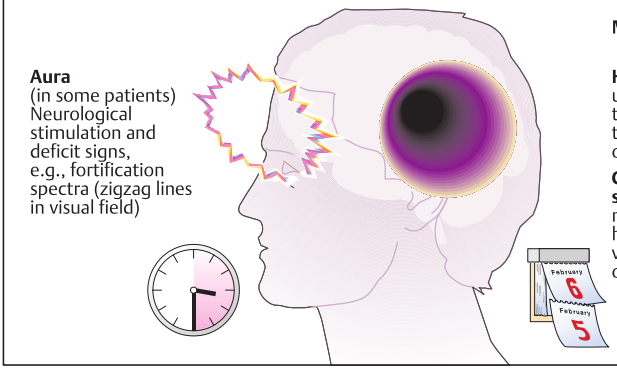
The sensory symptoms that accompany migraine attacks along with the aura result from neuronal dysfunction. It is now assumed that this starts in the brainstem. Ion channel dysfunction due to a genetic variation in its amino acid sequence may be present, and this becomes apparent under certain conditions.

► **Treatment and prophylaxis.** Treatment is symptomatic (► Fig. 40.4**C**). It is complicated by the accompanying symptoms of nausea and vomiting, which interfere with oral drug absorption. **Metoclopramide** or domperidone are dopamine D_2 receptor antagonists (see p. 128), which have a good antiemetic action in migraine. They also speed up gastric emptying, thus improving absorption of oral analgesics. **Acetylsalicylic acid** (ASA, 1000 mg, especially effective when given by injection as the lysine salt) is a proven remedy for migraine headache. Acetaminophen (1000 mg, available in suppository form) and nonsteroidal anti-inflammatory drugs such as ibuprofen, diclofenac, or naproxen are also helpful.

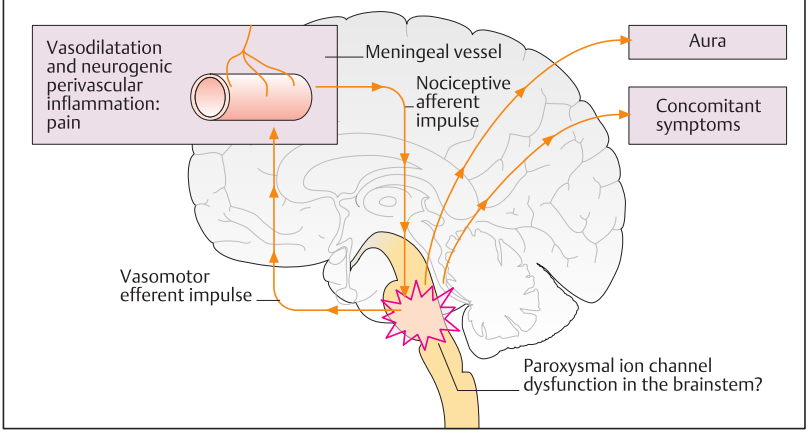
Triptans can achieve a somewhat better effect than acetylsalicylic acid. **Sumatriptan** is the prototype. They also improve the concomitant symptoms of nausea, vomiting, and sensory hypersensitivity. Triptans stimulate the serotonin receptor subtypes 5-HT_{1B} and 5-HT_{1D} (p. 132). In this way they inhibit neuronal release of proinflammatory neuropeptides and constrict meningeal arteries. Unlike ASA, the triptans are ineffective in ordinary tension headaches. A possible side effect is a sensation of chest tightness. Triptans are contraindicated in the presence of vascular diseases (e.g. coronary heart disease). Successor triptans include almo-, ele-, frova-, nara-, riza-, and zolmitriptan. The importance of the **ergot alkaloids** ergotamine and dihydroergotamine, is diminishing. They act as agonists at 5-$HT_{1B/D}$ receptors and a number of other receptors. Side effects include nausea and vomiting, and, with chronic use, persistent headache, circulatory disorders (ergotism), and fibrosis. Triptans and ergot alkaloids (p. 144) must not be given together.

The β-blockers metopropol and propranolol, and also flunarizine (whose molecular mode of action is unclear) and valproate, which is primarily an antiepileptic drug, have been shown to be useful in the prevention of attacks.

A. Symptoms



B. Pathophysiology



C. Therapy and prophylaxis

Nonopioid analgesics

Acetylsalicylic acid p.o., i.v.
or
acetaminophen p.o., rectal

+

Antiemetic

Metoclopramide p.o., rectal, i.m., i.v.

Triptans
5-HT$_{1B/D}$ agonists

e.g., sumatriptan p.o., rectal, nasal, s.c.

Also improve nausea and vomiting

Contraindication: vascular disease

Ergot alkaloids, agonists at 5-HT$_{1B/D}$, D$_2$, α_1+α_2, etc.

(Dihydro-)ergotamine
s.c.
i.m.
p.o.
rectal

Nausea, vomiting; with chronic use circulatory disorders, persistent headache

+

Antiemetic

For prophylaxis: first choice: β-blocker (metoprolol, propranolol) or flunarizine

Fig. 40.4

Emesis and Antiemetics

In emesis the stomach empties in a retrograde manner. The pyloric sphincter is closed while cardia and esophagus relax to allow gastric contents to be propelled orad by a forceful synchronous contraction of abdominal wall muscles and diaphragm. Closure of the glottis and elevation of the soft palate prevent entry of vomitus into the trachea and the nasopharynx. As a rule, there is prodromal salivation or yawning. Coordination between these different stages depends on the **medullary center for emesis,** which can be activated by diverse stimuli. These are conveyed via the **vestibular apparatus, visual, olfactory,** and **gustatory inputs,** as well as **viscerosensory afferents** from the upper alimentary tract. **Psychic stress** may also activate the emetic center. The mechanisms underlying **motion sickness** (kinetosis, sea sickness) and vomiting during pregnancy are still unclear.

Polar substances cannot reach the emetic center itself because it is protected by the blood–brain barrier. However, they can indirectly excite the center by activating chemoreceptors in the area postrema or receptors on peripheral vagal nerve endings.

► **Antiemetic therapy.** Vomiting can be a useful reaction enabling the body to eliminate an orally ingested poison. Antiemetic drugs are used to prevent kinetosis, pregnancy vomiting, cytotoxic drug-induced or postoperative vomiting, as well as vomiting due to radiation therapy.

Motion sickness. Effective prophylaxis can be achieved with the parasympatholytic scopolamine (p. 126) and H_1 antihistamines (p. 130) of the diphenylmethane type (e.g., diphenhydramine, meclizine). Antiemetic activity is not a property shared by all parasympatholytics or antihistamines. The efficacy of the drugs mentioned depends on the actual situation of the individual (gastric filling, ethanol consumption), environmental conditions (e.g., the behavior of fellow travelers), and the type of motion experienced. The drugs should be taken 30 minutes before the start of travel and repeated every 4–6 hours. Scopolamine applied transdermally through an adhesive patch 6–8 hours before travel can provide effective protection for up to 3 days.

Pregnancy vomiting is prone to occur in the first trimester; thus, pharmacotherapy would coincide with the period of maximal fetal vulnerability to chemical injury. Accordingly, antiemetics (antihistamines), or neuroleptics if required should be used only when continuous vomiting threatens to disturb electrolyte and water balance to a degree that places the fetus at risk.

► **Drug-induced vomiting.** To prevent vomiting during anticancer chemotherapy (especially with cisplatin), effective use can be made of 5-HT_3 receptor antagonists (e.g., *ondansetron, granisetron,* and *tropisetron).* They are used to prevent vomiting that occurs directly after cytostatic administration. **Aprepitant** is also useful for cytostatic-induced emesis. This drug blocks the neurokinin receptor through which substance P activates the vomiting center. Unlike the "setrons," it is also effective against late vomiting following a period of latency. Fosaprepitant is a precursor of aprepitant and is given intravenously. Other possible agents are dopamine D_2 antagonists such as metoclopramide, which may cause early dyskinesia, and domperidone, which does not penetrate the CNS. Neuroleptics, e.g., levomepromazine and haloperidol (p. 232), may also be used, with or without glucocorticoids (dexamethasone). Anticipatory vomiting ahead of the next chemotherapy cycle is psychogenic and can be managed by behavior therapy or anxiolytic drugs of the benzodiazepine type.

Emesis following **surgery,** during **radiotherapy,** due to **uremia,** and in diseases accompanied by **elevated intracranial pressure** is also treated with neuroleptics or metoclopramide.

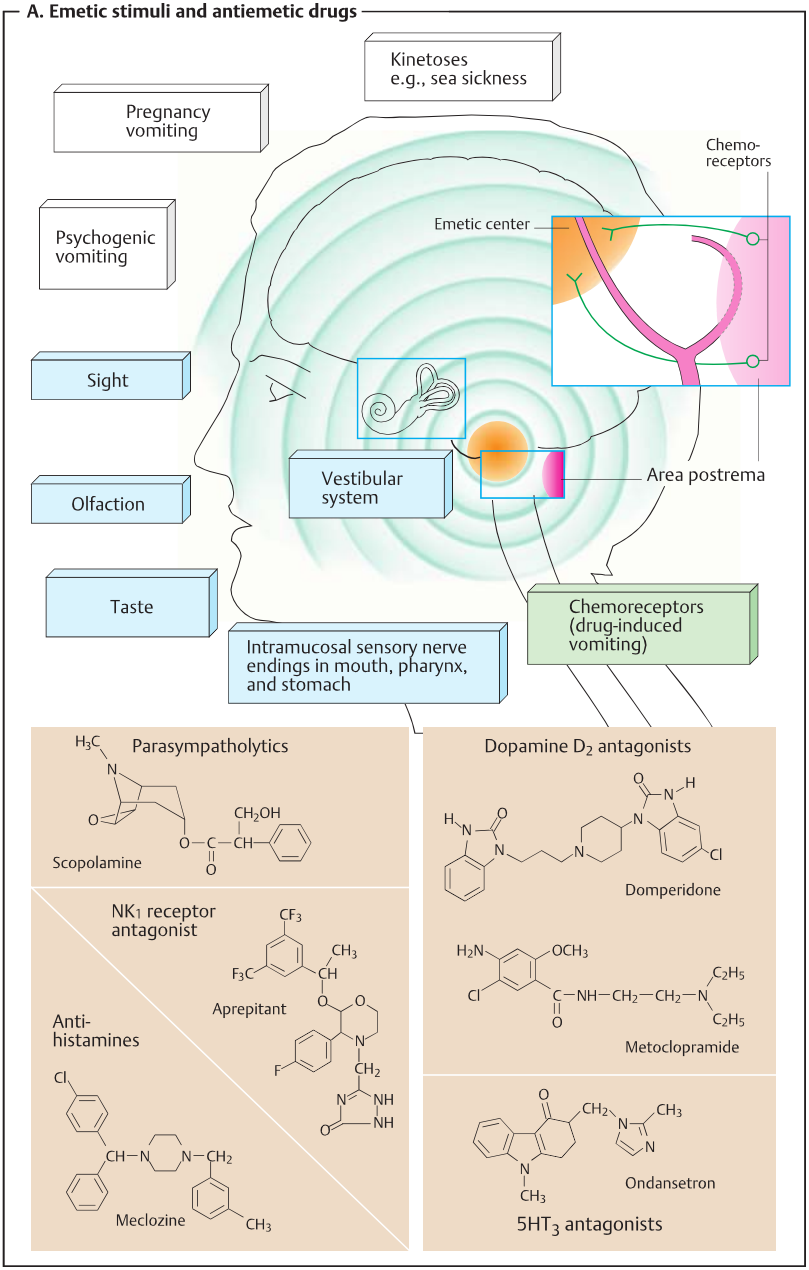

A. Emetic stimuli and antiemetic drugs
Kinetoses
e.g., sea sickness
Pregnancy
vomiting
Psychogenic
vomiting
Sight
Olfaction
Taste
Chemo-
receptors
Emetic center
Area postrema
Vestibular
system
Chemoreceptors
(drug-induced
vomiting)
Intramucosal sensory nerve
endings in mouth, pharynx,
and stomach
Parasympatholytics
Scopolamine
Dopamine D2 antagonists
Domperidone
NK1 receptor
antagonist
Aprepitant
Anti-
histamines
Meclozine
Metoclopramide
Ondansetron
5HT3 antagonists

Fig. 40.5

Sleep Disorders and Hypnotics

Sleep is a period of rest for the CNS and should amount to about 7 hours daily for humans. Sleep disorders leading to a **chronic sleep deficit** are common; they reduce performance and interfere with well-being. Insomnia can have a variety of causes and these should be clarified before medication is prescribed. These include: (a) severe mental stress; (b) poor external conditions in the bedroom (too noisy, too warm, etc.); (c) an inappropriate lifestyle, for instance eating a heavy meal or drinking strong coffee before bedtime or a lack of exercise; (d) serious diseases associated with pain or a troublesome cough.

Depending on circumstances, the therapist will attempt to help. In cases (b) and (c) prescription of a **hypnotic** is **not** justified. The doctor can only explain the situation to someone affected by (b) and suggest changes. People who fall into the (c) group should be strongly advised to correct their lifestyle for a healthier one. However, this approach will be successful only in patients with insight.

Prescribing a hypnotic can be justified when the sleep disorder is due to severe worry or psychological stress. There should be no hesitation in prescribing an effective and longer-acting hypnotic for a severely ill patient.

A basic requirement of a hypnotic is not just that it works reliably but also that it has a broad therapeutic safety margin. The barbiturates are regarded as good hypnotics but they have been abandoned because they were often misused for suicidal purposes. The introduction of the **benzodiazepines** (see p. 222) and their use as hypnotics is an advance, because "it's impossible to kill oneself with them." **Brotizolam** is a short-acting benzodiazepine hypnotic. **Triazolam,** another short-acting hypnotic, has caused apparently paradoxical excitatory states, anxiety, and aggressive behavior. In some jurisdictions it is subject to controlled drug prescribing rules. **Nitrazepam, temazepam, lorazepam,** and a few other derivatives are regarded as intermediate-acting hypnotics. Depending on the dosage, these preparations have a calming and sedative effect and induce sleep, eventually irresistibly. Overdose is not associated with central respiratory depression. **Flumazenil** is a specific antidote.

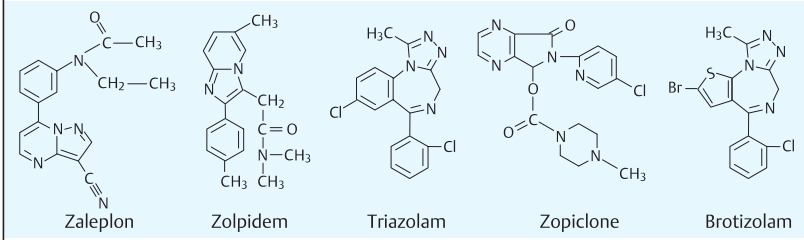
Substances that have the same mechanism of action as the benzodiazepines but with a different chemical structure are also good hypnotics and are referred to humorously as **Z-substances** because their nonproprietary names all start with "Z." There are three brands of **zolpidem** and two brands of **zopiclone** on the market. Up to 2014, **zaleplon** was available only under its original name (Sonata), but generic versions are now on the market.

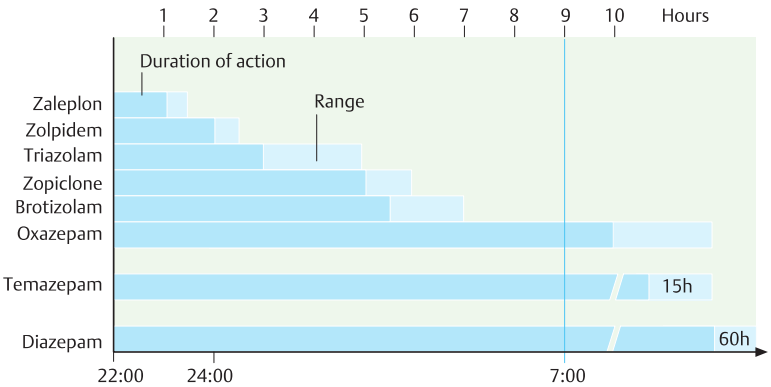
Melatonin is produced in the pineal gland and controls circadian rhythm. It is secreted more at night and has a weak action in the treatment of primary sleep disorders.

All of the hypnotics mentioned so far are prescription drugs. However, there is a large number of "over-the-counter" preparations. These include several sedating **antihistamines,** such as doxylamine and diphenhydramine, which have weak sedative and hypnotic side effects. They are used as "sleeping pills" because of this side effect. These substances are not recommended but there are numerous products on the market.

A number of **herbal products** may be mentioned: valerian, hops, lemon balm, and others. *These phytotherapeutic agents do not have any scientifically demonstrable effect.* For some people, taking them is part of their bedtime ritual. The same applies to **homeopathic preparations**. This shows that sleep disorders respond very well to **psychotherapeutic approaches**. Behavioral therapy using buzzwords like sleep hygiene, stimulus control therapy, and sleep restriction allow patients to do without drugs and cure the problem on their own.

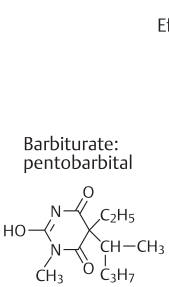
A. Hypnotics





Duration of action of short- and intermediate-acting hypnotics projected onto nighttime

B. Concentration dependence of effects



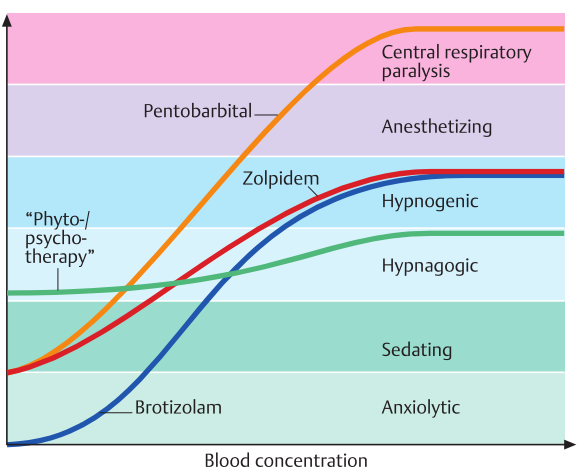


Fig. 40.6

Local Treatment of Glaucoma

Glaucoma signifies a disease of the optic nerve associated with destruction of neurons and atrophy of the optic nerve. This results in shrinking of the visual field. Often, the patient only becomes aware of this at a late stage because the peripheral areas are affected initially and the central visual field subsequently.

The risk factors statistically are increasing age, dark skin color, family history, and increased intraocular pressure (normally 10–21 mmHg in adults). It should be noted that increased intraocular pressure (IOP) is a risk factor but not a necessary precondition for glaucoma, which can occur even when the IOP is normal. It is obvious that the IOP is the only risk factor that can be modified.

Intraocular pressure can be reduced using drugs with different mechanisms of action. IOP reflects the ratio of production and outflow of aqueous humor. Aqueous humor is secreted by the epithelial cells of the ciliary body and, following passage through the trabecular meshwork, is drained via the canal of Schlemm (blue arrows in ▶ Fig. 41.1**A**). This route is taken by 85–90% of aqueous humor; a smaller portion enters the neighboring uveoscleral vessels and, thus, the venous system. In **open-angle glaucoma,** passage of aqueous humor through the trabecular meshwork is impeded so that drainage through the Schlemm canal becomes inefficient. In this type of glaucoma, there is no firm connection between the raised IOP and the optic nerve damage. The much rarer primary **angle-closure glaucoma** features a narrowed iridocorneal angle with the iris directly against the posterior surface of the cornea, blocking the way to the Schlemm canal.

For topical therapy of **open-angle glaucoma,** the following groups of drugs can be used:

For reducing production of aqueous humor, β-blockers (e.g., timolol), α_2-agonists (clonidine, brimonidine), and inhibitors of carbonic anhydrase (dorzolamide, brinzolamide).

For promoting drainage through the trabecular meshwork to the canal of Schlemm, parasympathomimetics (e.g., pilocarpine) can be used, and through the uveoscleral route, prostaglandin derivatives. Pilocarpine excites the ciliary muscle and the pupillary sphincter. The contraction of both muscles widens the geometrical arrangement of trabeculae, resulting in improved drainage of aqueous humor. However, this is associated with impaired vision, with the eye adjusted for near vision and reduced vision at twilight. Uveoscleral drainage is augmented by the prostaglandin derivatives latanoprost, bimatoprost, and tafluprost. These substances can be used for topical monotherapy or combined with other active principles. A peculiar side effect is notable: dark pigmentation of the iris and eyelashes.

The therapy of **angle-closure glaucoma** involves chiefly reduction of aqueous humor production (osmotic agents, β-blockers) and surgical procedures.

The topical application of pharmaceuticals in the form of eye-drops is hampered by a pharmacokinetic problem. The drug must penetrate from the ocular surface (cornea and conjunctiva) to the interior of the eye (▶ Fig. 41.1**B**). The applied drug concentration is diluted by lacrimal fluid and drains via the tear duct to the nasal mucosa, where the drug may be absorbed. During permeation through the cornea, transport through blood vessels takes place. The drug concentration reaching the anterior chamber is diluted by aqueous humor and, finally, drug molecules are also transported away via the Schlemm canal. In order to reach the required concentrations at the target site (10^{-8} to 10^{-6} M, depending on the substance), the concentration needed in the eye drops is ~10^{-2}M (equivalent to ~0.5 mg per droplet, depending on molecular weight). The amount of drug contained in a single drop is large enough to elicit a general reaction with systemic use. Even when applied properly, eye drops can therefore evoke side effects in the cardiovascular system or the bronchial space. This possibility leads to corresponding contraindications.

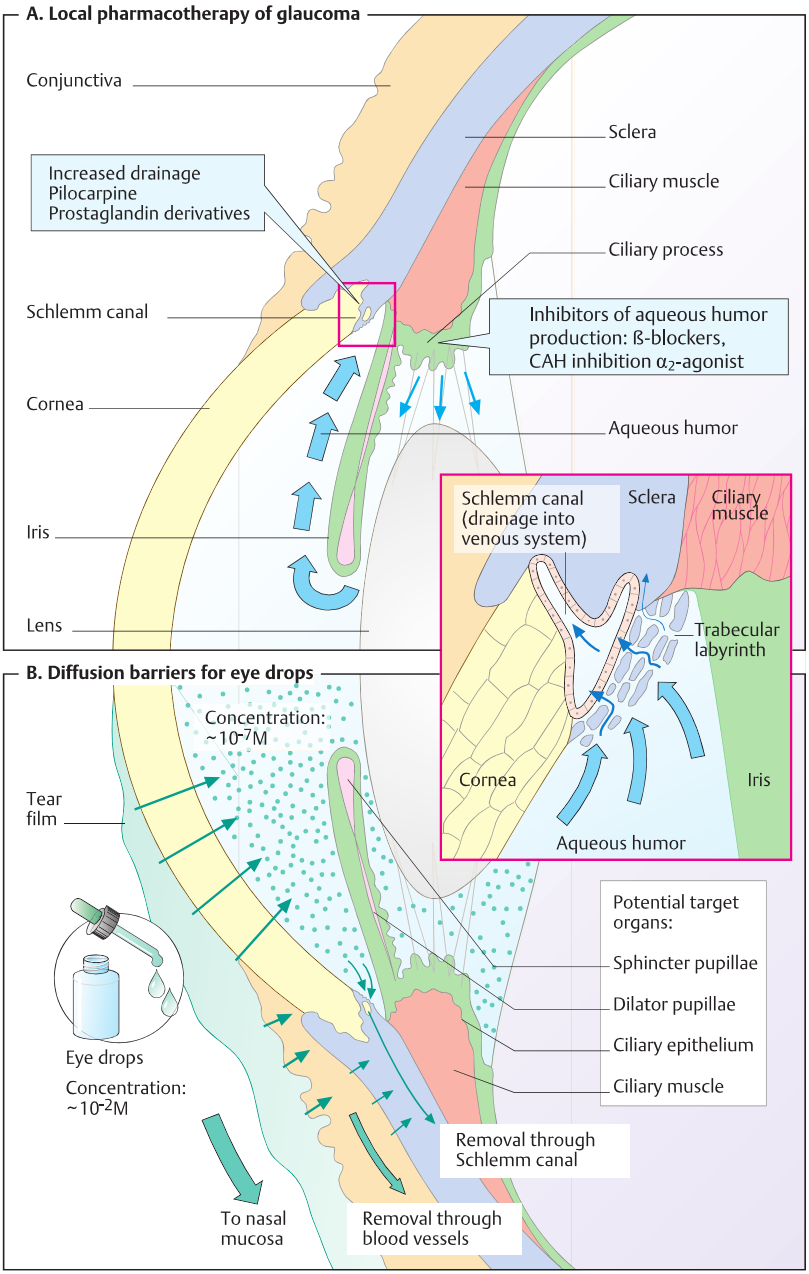

A. Local pharmacotherapy of glaucoma
Conjunctiva
Sclera
Increased drainage
Pilocarpine
Prostaglandin derivatives
Ciliary muscle
Ciliary process
Schlemm canal
Inhibitors of aqueous humor production: ß-blockers, CAH inhibition α2-agonist
Cornea
Aqueous humor
Iris
Lens
Schlemm canal (drainage into venous system)
Sclera
Ciliary muscle
Trabecular labyrinth
Cornea
Iris
Aqueous humor
B. Diffusion barriers for eye drops
Concentration: ~10-7M
Tear film
Potential target organs:
Sphincter pupillae
Dilator pupillae
Ciliary epithelium
Ciliary muscle
Eye drops
Concentration: ~10-2M
Removal through Schlemm canal
To nasal mucosa
Removal through blood vessels

Fig. 41.1

Osteoporosis

Osteoporosis is defined as a generalized decrease in bone mass (osteopenia, **A**) that equally affects bone matrix and mineral content and is associated with a change in the architecture of spongy bone. This condition predisposes to collapse of vertebral bodies and bone fractures with trivial trauma (e.g., hip fractures). In female postmenopausal osteoporosis, part of the bone mass that is estrogen-dependent is initially lost within a few years. This is followed by bone atrophy (senile osteoporosis), which also occurs in old age in men.

Bone substance is subject to continual remodeling. The equilibrium between bone formation and bone resorption is regulated in a complex manner: a remodeling cycle is initiated by osteoblasts when these stimulate uninucleated osteoclast precursor cells to fuse into large multinucleated cells. Stimulation occurs by direct cell-to-cell contact between osteoblasts and osteoclast precursor cells and is mediated by the RANK ligand (RANK = receptor activator of NFκB) on the surface of osteoblasts and its receptor on the osteoclasts (or their precursors). These processes are inhibited by a protein secreted by osteoblasts (osteoprotegerin). This acts like a fake RANK to divert RANKL from its actual target RANK. Estrogens increase the production of osteoprotegerin, thereby inhibiting osteoclast activation. The osteoclast creates an acidic milieu, enabling minerals to be solubilized, and then phagocytoses the organic matrix. After a certain amount of bone mass has been broken down, osteoblasts take over bone formation. Depending on the quantitative ratio between resorption and formation, bone mass increases (in childhood and adolescence), decreases (in old age), or remains steady. Hormones regulate these events.

Parathyroid hormone (**parathormone**) stimulates bone remodeling. In hypocalcemia, secretion is increased, resulting in enhanced liberation of Ca^{2+} and a loss of bone mass. Conversely, parathormone deficiency may cause adynamic bone disease. In osteoporosis, bone growth can be induced by once-daily injection of parathormone or teriparatide, a shortened derivative. This is probably because the concentration pulses stimulate osteoblasts to matrix synthesis but not to osteoclast activation. **Calcitonin** transfers active osteoclasts into a resting state. Calcitonin given therapeutically relieves pain associated with neoplastic bone metastases and vertebral body collapse. **Estrogens** diminish bone resorption by (a) inhibiting activation of osteoclasts by osteoblasts and (b) promoting apoptosis of osteoclasts.

Postmenopausal osteoporosis can be prevented by administration of calcium (1000 mg Ca^{2+}) and vitamin D (1000 U/day). Use of estrogen/progestin in postmenopausal women has not been accepted because of the increased incidence of breast cancer, thromboembolism, and other harmful effects (p. 248).

Bisphosphonates (N-containing) structurally mimic endogenous pyrophosphate (see formulae), and like the latter are incorporated into the mineral substance of bone. During phagocytosis of the bone matrix, they are taken up by osteoclasts. There, the *N*-containing bisphosphonates inhibit prenylation of G-proteins and thus damage the cells. Accordingly, osteoclast activity levels are lowered by **alendronate** and **risedronate,** while osteoclast apoptosis is promoted. The result is a reduction in bone resorption and a decreased risk of bone fractures.

Raloxifene (p. 252) exerts an estrogen-like effect on bone, while acting as an estrogen antagonist in the uterus and breast tissue. In terms of fracture prophylaxis, its effectiveness appears inferior to that of bisphosphonates.

Long-term use of **strontium ranelate** with incorporation of strontium cations in bone inhibits bone resorption and promotes bone formation in an as yet unexplained manner.

Denosumab, a monoclonal IgG antibody, blocks RANK ligand, in principle imitating physiological RANKL inhibition by osteoprotegerin (see above).

Dibotermin and **eptotermin** are osteogenic growth factors produced by recombinant technology that are implanted surgically.

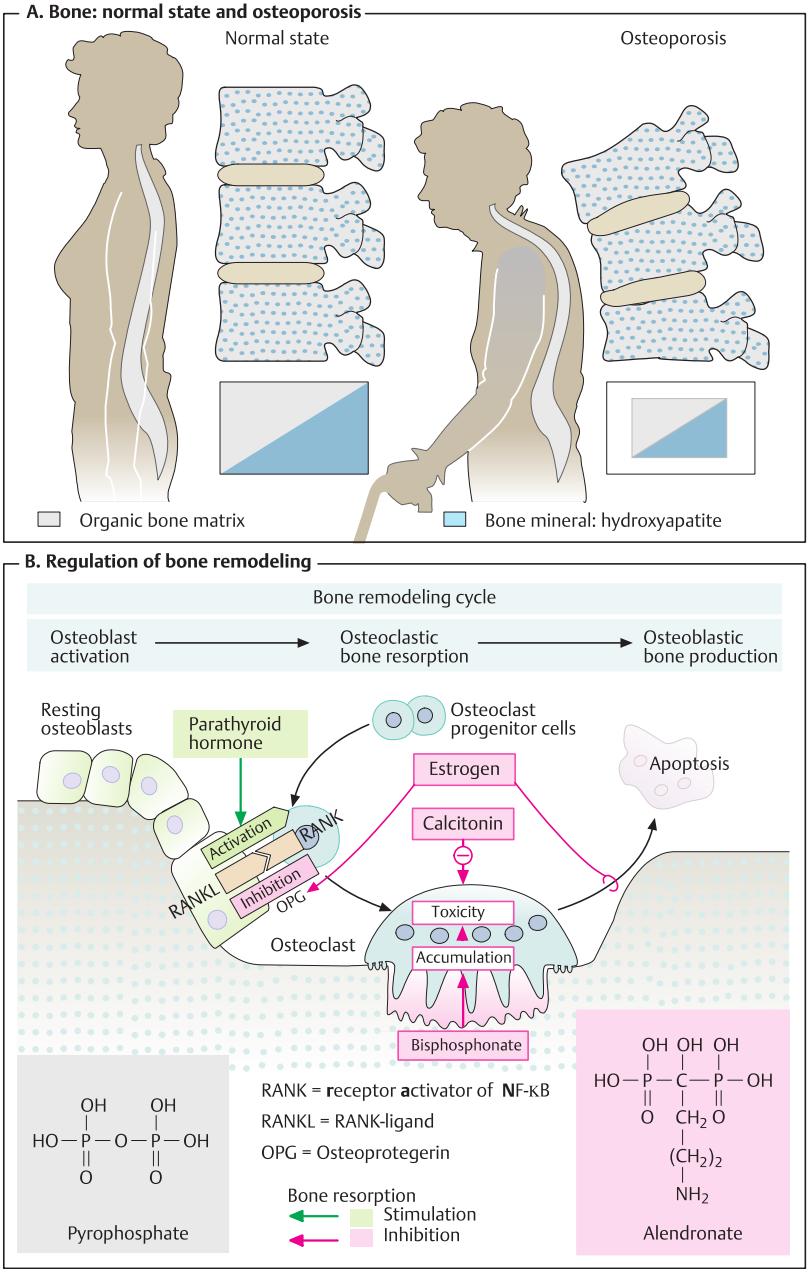

A. Bone: normal state and osteoporosis
Normal state
Osteoporosis
Organic bone matrix
Bone mineral: hydroxyapatite
B. Regulation of bone remodeling
Bone remodeling cycle
Osteoblast activation
Osteoclastic bone resorption
Osteoblastic bone production
Resting osteoblasts
Parathyroid hormone
Osteoclast progenitor cells
Estrogen
Apoptosis
Calcitonin
Activation
RANK
RANKL
Inhibition
OPG
Toxicity
Osteoclast
Accumulation
Bisphosphonate
RANK = receptor activator of NF-κB
RANKL = RANK-ligand
OPG = Osteoprotegerin
Bone resorption
Stimulation
Inhibition
Pyrophosphate
Alendronate

Fig. 42.1

Gout and its Treatment

Purines are metabolized to uric acid via hypoxanthine and xanthine. These intermediates are water-soluble and are easily eliminated by the kidneys; uric acid is less soluble and can just be eliminated adequately in persons with healthy metabolism. **Gout** results if there is an imbalance between the amount of uric acid produced and the total quantity of uric acid excreted. Gout is characterized by increased blood urate levels. Urate crystals precipitate in parts of the body that provide poor conditions for urate solubility, such as synovial fluid, and where the temperature is lower than normal body temperature. This provokes an acute **gout attack.** The base of the big toe is affected particularly often. Like other crystals, urate crystals provide a strong stimulus for neutrophil granulocytes and macrophages. Neutrophils are attracted and phagocytose this indigestible material. In the process, the neutrophils release proinflammatory cytokines. Macrophages also phagocytose the crystals, are thereby injured, and liberate lysosomal enzymes that likewise promote inflammation and attack tissues. As a result, an acute and very painful gout attack may develop.

The **therapy of gout** is twofold: (1) treatment of the acute attack and (2) chronic lowering of hyperuricemia. The acute attack demands prompt action to relieve the patient from their painful state. The classical remedy (even used by Hippocrates) is **colchicine,** an alkaloid from the autumn crocus *(Colchicum autumnale).* This substance inhibits the function of microtubules in the phagocytic cells and hence their mobility. This prevents phagocytosis of the crystals, which is the basis of the extremely painful process.

A gout attack can also be aborted by **nonsteroidal anti-inflammatory drugs** such as indomethacin or diclofenac.

Chronic lowering of blood urate levels to below 6 mg/100 mL requires:

a) An appropriate **diet:** foods high in purines such as offal must be avoided. Purines are found in cell nuclei, so eggs (only one nucleus per egg!) and dairy products may be consumed freely.

b) **Uricostatic agents** such as **allopurinol** that inhibit xanthine oxidase, which catalyzes uric acid production. Purine metabolism is halted at the intermediate hypoxanthine and xanthine stages and these intermediates can be eliminated renally. Under the influence of allopurinol, the hyperuricemia improves, ideally to a blood urate level of 3–6 mg/dL Allopurinol is given orally (300–800 mg/day). Apart from rare allergic reactions it is well tolerated and is the drug of choice for gout prophylaxis. Gout attacks may occur at the start of therapy but they may be prevented by concurrent administration of colchicine (1–1.5 mg/day). Febuxostat is a xanthine oxidase inhibitor with a different structure and can be used in the case of intolerance of allopurinol or benzbromarone (see below).

► **Uricosuric medications.** Uricosuric medications such as **probenecid** or **benzbromarone** (100 mg/day) promote renal excretion of uric acid. They saturate the organic acid transport system in the proximal renal tubules, making it unavailable for urate reabsorption. When underdosed, they inhibit only the acid secretory system, which has a smaller transport capacity. Urate elimination is then inhibited and a gout attack is possible. In patients with urate stones in the urinary tract, uricosurics are contraindicated.

► **Uricolytics.** Nonprimates are able, via the enzyme urate oxidase, to metabolize uric acid to allantoin, a product with better water solubility and faster renal elimination. **Rasburicase,** a recombinant urate oxidase, can be given by infusion in patients with malignant neoplasms, in whom chemotherapy is liable to generate a massive amount of uric acid.

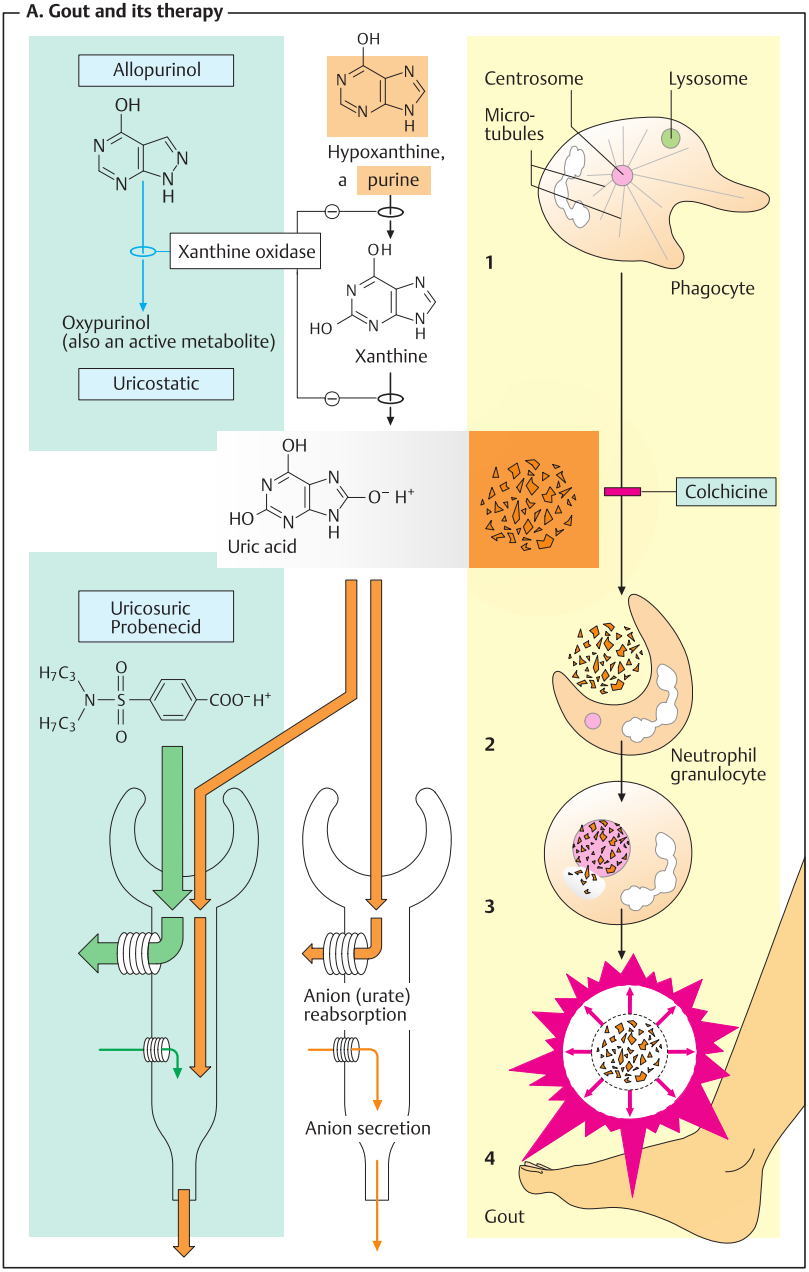

A. Gout and its therapy
Allopurinol
Oxypurinol
(also an active metabolite)
Uricostatic
Xanthine oxidase
Hypoxanthine,
a purine
Xanthine
Uric acid
Uricosuric
Probenecid
Anion (urate)
reabsorption
Anion secretion
Centrosome
Lysosome
Micro-
tubules
1
Phagocyte
Colchicine
2
Neutrophil
granulocyte
3
4
Gout

Fig. 43.1

Obesity—Causes, Sequelae and Therapeutic Approaches

Obesity is a growing medical problem in industrialized societies. Overweight persons are at increased risk of **metabolic disorders**, e.g., metabolic syndrome with high blood pressure, type II diabetes mellitus (p. 260) and **mechanical disorders** (osteoarthritis due to increased stress on joints). Being fat also involves psychosocial problems.

The body mass index (BMI) is used to quantify overweight and obesity (BMI = weight/[height^2]). The waist : hip ratio takes into account the fact that intra-abdominal mesenteric fat determines the risk of metabolic complications.

A glance at the **mechanisms that regulate food intake** will suggest possible pharmacological approaches. In terms of evolutionary biology, it was essential for existence that nature designed a strong drive to eat so that energy reserves would be built up in the form of stored fat "in times of plenty." This drive is both physical and psychological in nature.

The sensation of hunger arises in the "appetite center" in the hypothalamus. Its activity is controlled by signals from the CNS and peripheral organs. **Signals from the periphery** originate from:

- Metabolism: e.g., a fall in the blood glucose level.
- The stomach: release of ghrelin, an appetite-promoting peptide, from the mucosa when the stomach is empty. Note: ghrelin can also promote growth hormone release ("growth hormone release inducing") but is not identical with hypothalamic somatoliberin.
- The intestine: release of enteric hormones that reduce appetite during digestion, e.g., glucagon-like peptide, which also promotes insulin secretion (p. 262).
- Adipose tissue: release of messenger substances that reduce appetite (adipokines), e.g., leptin when adipose tissue mass is increased.

In the CNS, norepinephrine and serotonin reduce appetite, while endocannabinoids increase it. Strong psychological motivation exists because eating activates the reward system and produces a sensation of pleasure. There are also conditioned (unconsciously learned) behavior patterns: pleasant environments and situations that are associated with eating generate a desire to eat even when there is no physical need to do so.

Currently, there are no recommended pharmacological measures for weight loss. Anorectic agents or appetite suppressants such as **sibutramine** are inhibitors of neuronal norepinephrine and/or serotonin reuptake derived from methamphetamine (p. 112). They are encumbered with cardiovascular side effects and are regarded as obsolete.

It is well known that Δ^9-tetrahydrocannabinol, the active ingredient of hashish and marijuana, has other actions besides its effect on mood. These include increased appetite, mediated by stimulation of cannabinoid receptors. Rimonabant blocks the CB_1 receptor subtype. When it is used for a prolonged period, a few kilograms are lost but psychiatric side effects are possible as a result of receptor blockade; these include anxiety, depression, and a risk of suicide. Sibutramine and rimonabant have been withdrawn from the European market but can be purchased on the internet.

Orlistat inhibits pancreatic lipase and hence fat digestion. Dietary fats, including fat-soluble vitamins, are excreted in the feces. Flatulence is common and continence may be impaired because of the "fatty stools" or steatorrhea. This forces the user to consume a low-fat diet. Before obese persons undergo this treatment, they should try to reduce the fat content of their diet by their own willpower.

Surgery to reduce the capacity of the stomach may be successful in treating extreme obesity.

A. Obesity: sequelae and therapeutic approaches

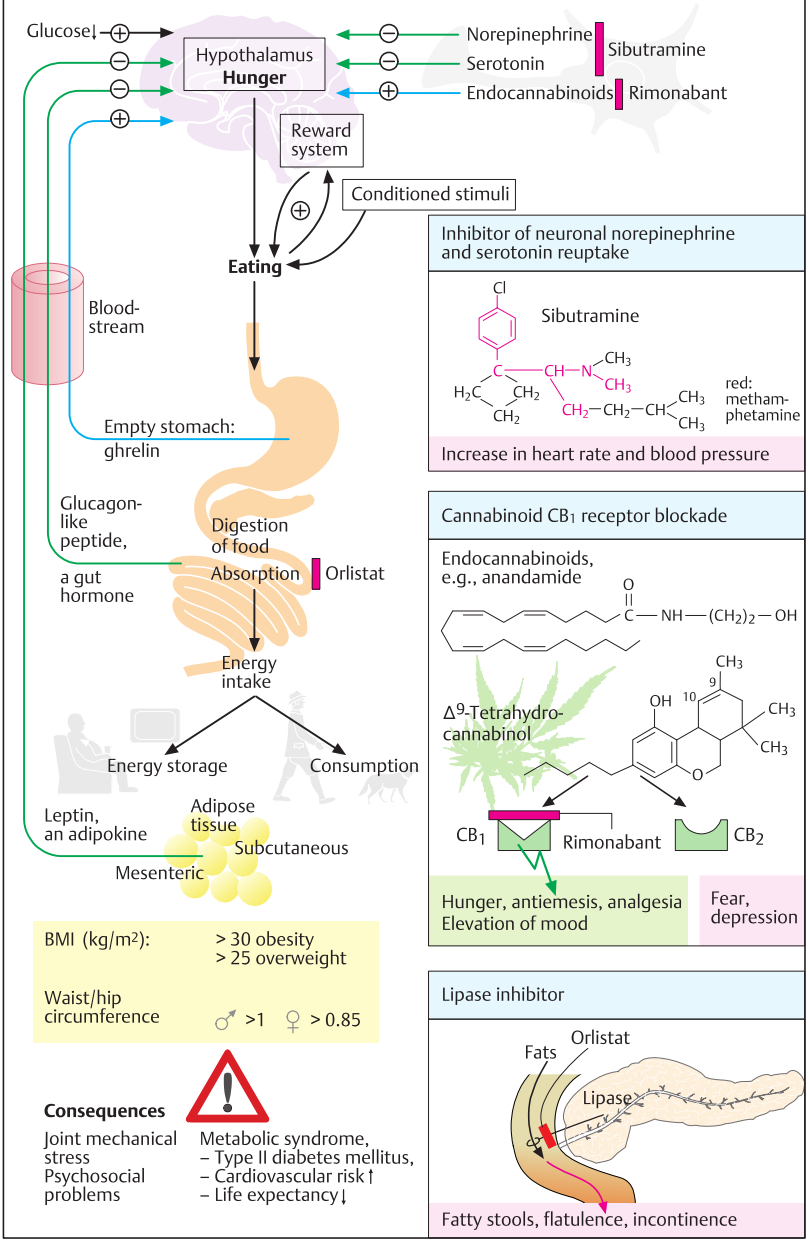


Fig. 43.2

Atopy and Antiallergic Therapy

Atopy denotes a hereditary predisposition for IgE-mediated allergic reactions. Clinical pictures include allergic rhinoconjunctivitis ("hay fever"), bronchial asthma, atopic dermatitis (neurodermatitis, atopic eczema), and urticaria. Evidently, differentiation of T-helper (T_H) lymphocytes toward the T_H2 phenotype is the common denominator. Therapeutic interventions are aimed at different levels to influence pathophysiological events (▶ Fig. 44.1**A**).

▶ **1 Specific immune therapy ("hyposensitization").** Hyposensitization with intracutaneous antigen injections is intended to shift T_H cells in the direction of T_H1.

▶ **2 Inactivation of IgE.** Inactivation of IgE can be achieved by means of the monoclonal antibody, omalizumab. This is directed against the Fc portion of IgE and prevents its binding to mast cells.

▶ **3 Stabilization of mast cells.** *Cromolyn* prevents IgE-mediated release of mast cell mediators. It is applied *locally* to conjunctiva, nasal mucosa, the bronchial tree (inhalation), and intestinal mucosa (absorption is almost nil with oral intake). Indications: *prophylaxis of hay fever, allergic asthma,* and *food allergies.*

▶ **4 Blockade of histamine receptors.** Allergic reactions are predominantly mediated by H_1 receptors. *H_1 antihistamines* (p. 130) are mostly used orally. Their therapeutic effect is often disappointing. Indications: allergic rhinitis *(hay fever).*

▶ **5 Blockade of leukotriene receptors.** Montelukast is an antagonist at receptors for (cysteinyl) leukotriene. Leukotrienes evoke intense bronchoconstriction and promote allergic inflammation of the bronchial mucosa. Montelukast is used for oral prophylaxis of bronchial asthma. It is effective in analgesia-induced asthma (p. 202) and exercise-induced bronchospasm. See also bronchial asthma (p. 356).

▶ **6 Functional antagonists of mediators of allergy.**

a) **α-Sympathomimetics,** such as naphazoline, oxymetazoline, and tetrahydrozoline, are applied topically to the conjunctival and nasal mucosa to produce local vasoconstriction. Their use should be short-term at most.

b) **Epinephrine,** given i.v., is the *most important drug in the management of anaphylactic shock:* it constricts blood vessels, reduces capillary permeability, and dilates bronchi.

c) **β_2-Sympathomimetics,** such as terbutaline, fenoterol, and salbutamol, are employed in *bronchial asthma,* mostly by inhalation, and parenterally in emergencies. Even after inhalation, effective amounts can reach the systemic circulation and cause side effects (e.g., palpitations, tremor, restlessness, hypokalemia). The duration of action of both salmeterol and formoterol, given by inhalation, is 12 hours. These long-acting β_2-mimetics are included in the treatment of severe asthma. Given at nighttime, they can prevent attacks that preferentially occur in the early morning hours.

d) **Theophylline** belongs to the methylxanthines. Its effects are attributed to both inhibition of phosphodiesterase (cAMP increase) and antagonism at adenosine receptors. In *bronchial asthma,* theophylline can be given orally for prophylaxis or parenterally to control the attack. Manifestations of overdosage include tonic-clonic seizures and cardiac arrhythmias (blood level monitoring).

e) **Glucocorticoids** (p. 242) have significant antiallergic activity and probably interfere with different stages of the allergic response. Indications: *hay fever, bronchial asthma* (preferably local application of analogues with high presystemic elimination, e.g., beclomethasone dipropionate, budesonide, flunisolide, fluticasone propionate); and *anaphylactic shock* (i.v. in high dosage) —a probably nongenomic action of immediate onset.

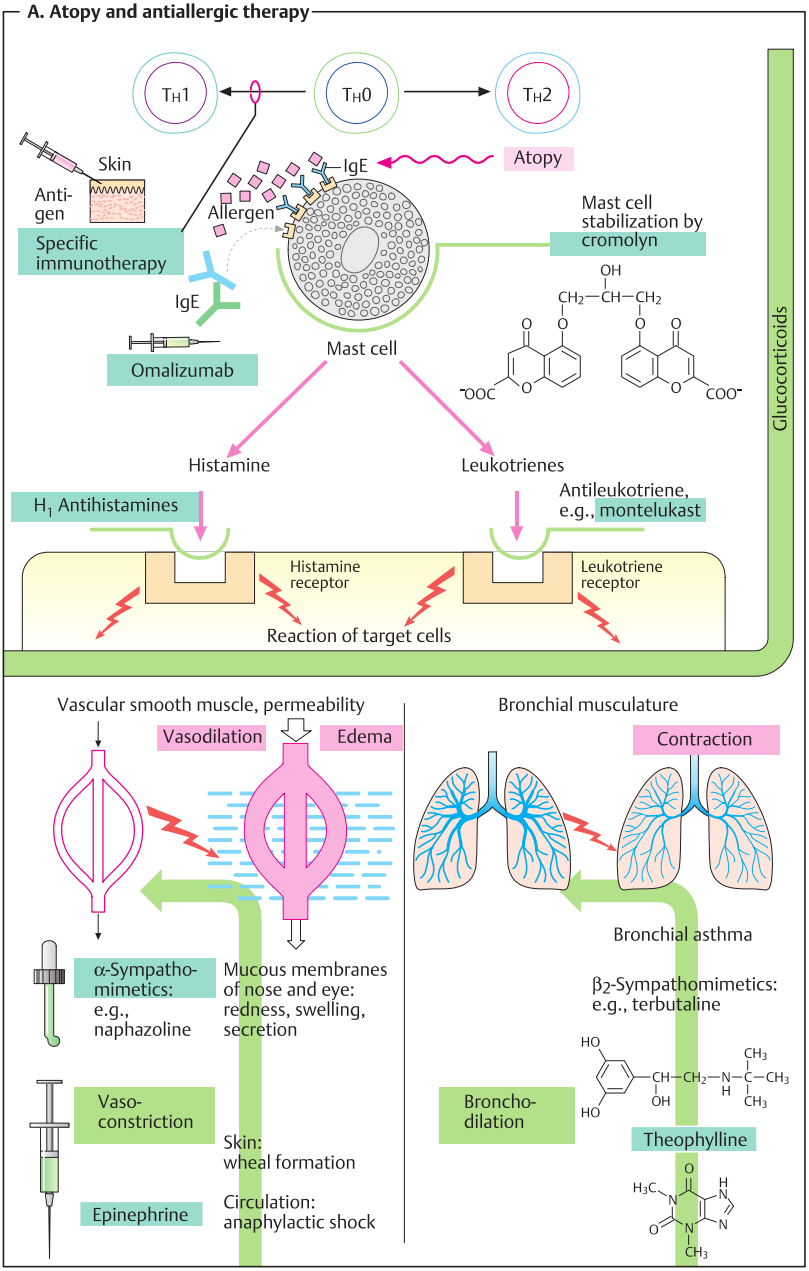

A. Atopy and antiallergic therapy
TH1
TH0
TH2
Skin
Anti-gen
Specific immunotherapy
Allergen
IgE
Atopy
Mast cell stabilization by cromolyn
IgE
Omalizumab
Mast cell
Glucocorticoids
Histamine
Leukotrienes
H1 Antihistamines
Antileukotriene, e.g., montelukast
Histamine receptor
Leukotriene receptor
Reaction of target cells
Vascular smooth muscle, permeability
Vasodilation
Edema
Bronchial musculature
Contraction
Bronchial asthma
α-Sympatho-mimetics: e.g., naphazoline
Mucous membranes of nose and eye: redness, swelling, secretion
β2-Sympathomimetics: e.g., terbutaline
Vaso-constriction
Skin: wheal formation
Broncho-dilation
Theophylline
Epinephrine
Circulation: anaphylactic shock

Fig. 44.1

Bronchial Asthma

► **Definition.** A recurrent, episodic shortness of breath caused by bronchoconstriction arising from airway inflammation and overreactivity.

► **Pathophysiology.** One of the main pathogenetic factors is allergic inflammation of the bronchial mucosa. For instance, leukotrienes that are formed during an IgE-mediated immune response exert a chemotactic effect on inflammatory cells. As the inflammation develops, bronchi become globally overreactive to spasmogenic stimuli. Thus, stimuli other than the original antigen(s) can act as triggers (► Fig. 44.1**A**), e.g., cyclooxygenase inhibitors (p. 202).

The tendency to bronchospasm follows a circadian rhythm and is usually most pronounced early in the morning.

► **Management.** Treatment (► Fig. 44.2**B**) aims to prevent attacks and allow normal working and leisure activities. Avoidance of attack triggers is an important prophylactic measure, though not always feasible, so pharmacological prophylaxis plays a key role in "controlling" the disease, meaning that attacks occur rarely or not at all and lung function is normal.

Drugs that inhibit allergic inflammatory mechanisms or reduce bronchial hyperreactivity attack crucial points in these processes. Bronchodilators provide symptomatic relief ("relievers") (cf. ► Fig. 44.2**A**).

Deterioration of lung function is often not adequately reflected by how patients feel subjectively, so regular self-measurement of the peak flow (typically in the morning) is advisable.

With the exception of the last step on the scheme described below, the drugs are delivered locally by inhalation, as this entails few side effects. Even though a considerable portion of the dose reaches the gastrointestinal tract, the most commonly used agents (glucocorticoids, β_2-sympathomimetics) have low bioavailability on account of their pronounced presystemic elimination.

The **step scheme** (► Fig. 44.2**B**) illustrates successive levels of pharmacotherapeutic management at increasing degrees of disease severity. This shows the preferred drugs for treatment of adults.

Step 1. Medications of first choice for the acute attack are *fast-acting, aerosolized β_2-sympathomimetics,* e.g., salbutamol or fenoterol. Their action occurs within minutes after inhalation and lasts for 4–6 hours.

Step 2. If β_2-mimetics are needed more frequently than twice a week, an inhaled glucocorticoid is added. Inhalational treatment with glucocorticoids must be administered regularly, improvement being evident only after several weeks. With proper inhalational use of glucocorticoids undergoing high presystemic elimination, concern about systemic adverse effects ("cortisone fear") is unwarranted. Possible local adverse effects are oropharyngeal candidiasis and dysphonia. To minimize the risk of candidiasis, the drug should be administered before morning or evening meals.

Anti-inflammatory therapy is the more successful the less use is made of as-needed β_2-mimetic medication.

Step 3. Continuous bronchodilator treatment is added. Preference is given to local use of a *long-acting inhaled β_2-mimetic*, e.g., salmeterol or formoterol (p. 354).

Step 4. The dose of inhaled glucocorticoid is increased.

Step 5. Treatment is further escalated either by additional systemic administration of a glucocorticoid or use of omalizumab, an antibody to IgE (p. 340).

Other prophylactic agents. Montelukast, a leukotriene receptor antagonist (p. 354) is an oral anti-inflammatory drug. It can be used as an alternative or supplement to a glucocorticoid.

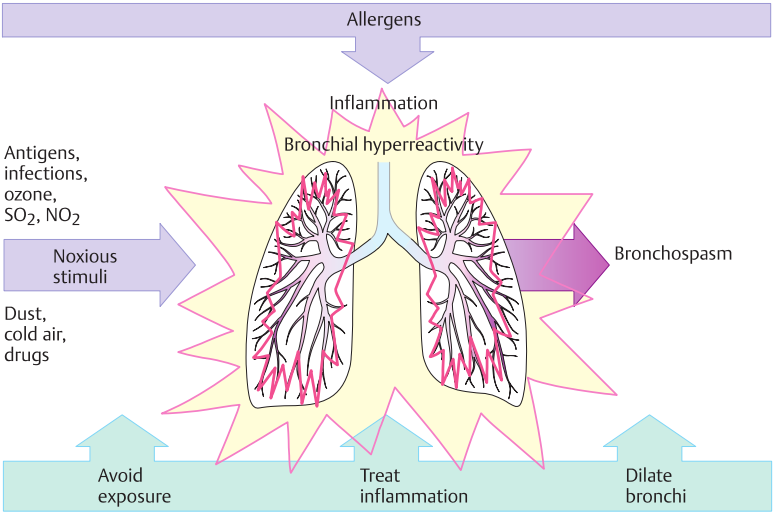
The *mast cell stabilizer cromoglicate* is also anti-inflammatory and is useful for milder forms of disease. It is given by inhalation and is well tolerated as the high polarity of its two carboxyl groups results in low bioavailability from the gastrointestinal tract.

Theophylline is a bronchodilator with a certain anti-inflammatory effect but must be given systemically. It has a narrow therapeutic range due to cardiac and central nervous system side effects and may now be considered obsolete.

Treatment of a severe asthma attack:

- Inhaled β_2-agonist in higher dose and at short intervals
- High-dose glucocorticoid orally
- Oxygen.

A. Bronchial asthma, pathophysiology and therapeutic approach



B. Bronchial asthma, 5-step treatment

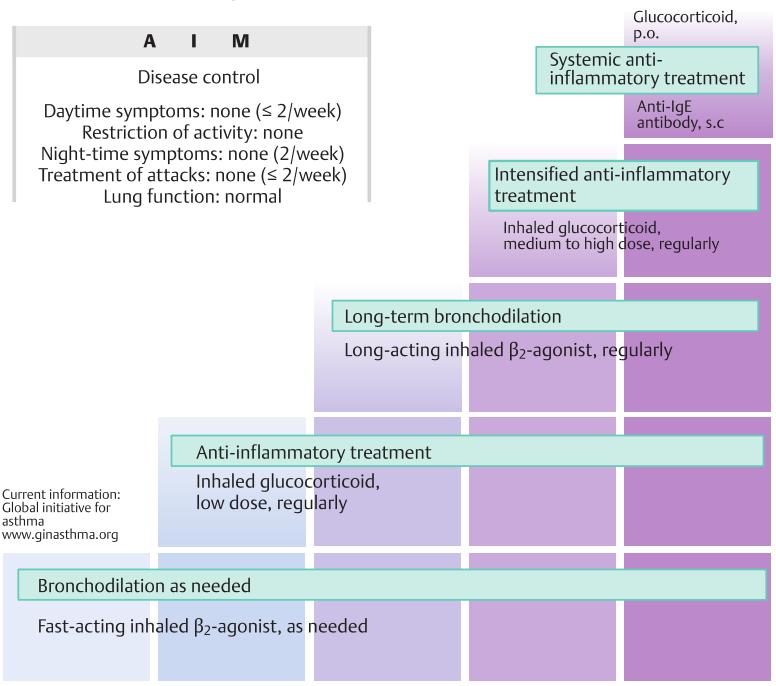


Fig. 44.2

COPD

► **Definition.** Chronic obstructive pulmonary disease is due to an abnormal inflammatory reaction of the respiratory tract to harmful gases and particles. COPD is characterized by a sustained and progressive reduction of airflow, which cannot be fully abolished by β_2-sympathomimetics.

► **Pathophysiology.** Cigarette smoking is the most frequent cause in affluent societies. This cause is in principle easy to eliminate, unlike exposure to an open fire in the single-room dwellings of the poor in the third world.

Sustained exposure to harmful gases and particles will lead to a chronic inflammatory reaction in the airways of any person. ► Fig. 44.3**A** lists the criteria for *chronic bronchitis*.

By contrast, *COPD* constitutes inappropriate and excessive inflammation. This is attributed to a *genetic predisposition* in affected persons. This explains why only some (15–20%) chronic cigarette smokers develop COPD. The very rare deficiency of α_1-antitrypsin, an endogenous protease inhibitor, is an example of a confirmed association between a tendency to COPD and a genetic predisposition. It can be managed by α_1-antitrypsin replacement.

The abnormal inflammatory reaction is associated with harmful remodeling processes (► Fig. 44.3**A**). *Pulmonary emphysema* ("puffed up" lung with large air-filled spaces) is only partially due to overinflation as a result of impaired exhalation. The walls (septa) of the small alveoli are destroyed so the alveoli merge to form larger spaces. As the capillaries within the septa are also destroyed, the resistance of the pulmonary vasculature increases. Hypoxic pulmonary arteriolar constriction (the Euler-Liljestrand mechanism) takes place. Chronic right heart strain leads in the long term to *cor pulmonale*.

Extrapulmonary signs appear as the disease progresses, e.g., cachexia, skeletal muscle atrophy, osteoporosis, depression. These may be interpreted as signs of chronic inflammation, possibly caused by inflammatory mediators washed out of the lungs.

Sudden and sometimes dramatic deteriorations in the shortness of breath (exacerbations) are greatly feared.

Respiratory failure and right heart failure are typical *causes of death* in COPD patients, in addition to lung cancer.

► **Management.** Since COPD is largely due to insidious and irreversible remodeling of the lung and small air passages, it is easy to understand why the disease only becomes apparent in middle age after a long smoking history and why the symptoms worsen if the patient continues to smoke.

This disastrous pathological progression can be halted only by preventing exposure, namely, smoking cessation.

Influenza vaccination and possibly pneumococcal vaccination protect against these respiratory tract infections with their risk of exacerbations.

The drugs shown in ► Fig. 44.3**B** are used according to severity grades A–D:

- *Inhaled bronchodilators*, rapid and short- or long-acting (once a day):
  - Muscarinic receptor antagonists, e.g., ipratropium or tiotropium (p. 124)
  - β_2-sympathomimetics, e.g., fenoterol and indacaterol (p. 106).

Both types of drugs can be combined. In view of the remodeling that has taken place, bronchodilators can confer a degree of alleviation but, unlike in asthma, they cannot produce normalization of the airflow.

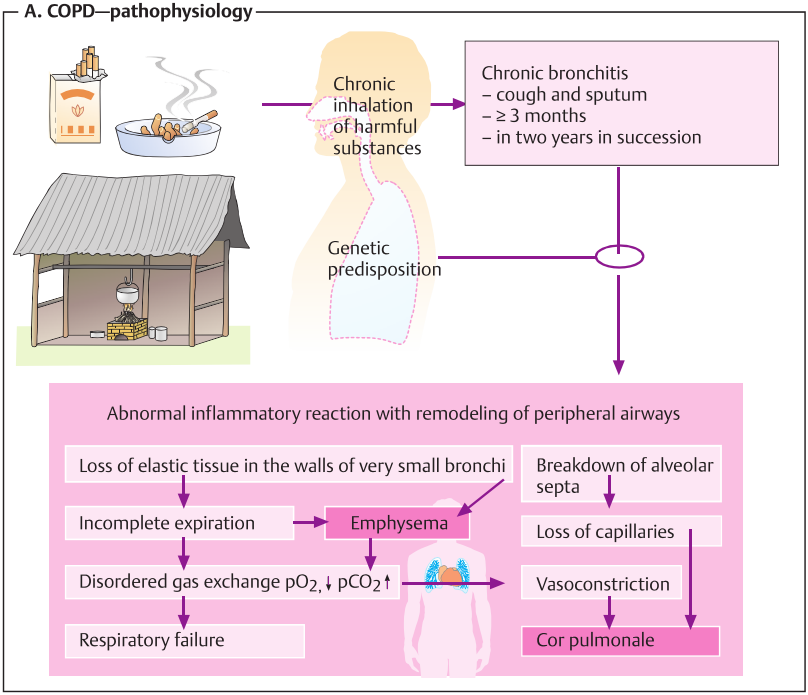
The following act as *anti-inflammatory agents*:

- Inhaled corticosteroids (p. 304), especially with the aim of preventing exacerbations; *systemic, high-dose corticosteroids* are used when exacerbation has occurred
- Possibly *roflumilast*, a phosphodiesterase-4 inhibitor given orally.

Medical treatment is supplemented by rehabilitation measures to improve physical strength.

Surgical procedures, e.g., removal of hyperinflated parts of the lung or even lung transplantation, may be necessary.

Oxygen may be given as a last resort to prevent suffocation.


A. COPD—pathophysiology
Chronic inhalation of harmful substances
Chronic bronchitis
– cough and sputum
– ≥ 3 months
– in two years in succession
Genetic predisposition
Abnormal inflammatory reaction with remodeling of peripheral airways
Loss of elastic tissue in the walls of very small bronchi
Breakdown of alveolar septa
Incomplete expiration
Emphysema
Loss of capillaries
Disordered gas exchange pO_2, ↓ pCO_2 ↑
Vasoconstriction
Respiratory failure
Cor pulmonale

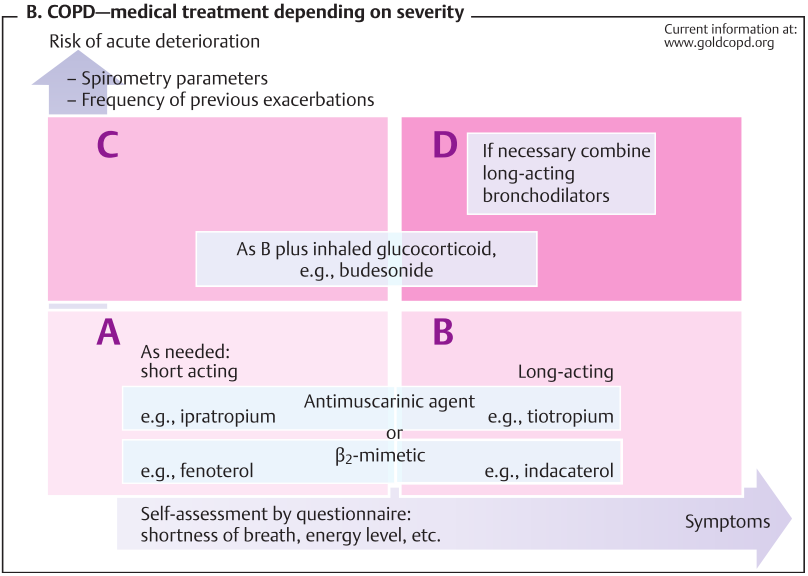

B. COPD—medical treatment depending on severity
Current information at:
www.goldcopd.org
Risk of acute deterioration
– Spirometry parameters
– Frequency of previous exacerbations
C
D
If necessary combine long-acting bronchodilators
As B plus inhaled glucocorticoid, e.g., budesonide
A
As needed: short acting
B
Long-acting
Antimuscarinic agent
e.g., ipratropium
e.g., tiotropium
or
β2-mimetic
e.g., fenoterol
e.g., indacaterol
Self-assessment by questionnaire: shortness of breath, energy level, etc.
Symptoms

Fig. 44.3

Rheumatoid Arthritis

Rheumatoid arthritis or **chronic polyarthritis** (▶ Fig. 44.4**A**) is a progressive inflammatory joint disease that intermittently attacks more and more joints, predominantly those of the fingers and toes. The probable cause of rheumatoid arthritis is a pathological reaction of the immune system. This malfunction can be promoted or triggered by various conditions, including genetic predisposition, age-related wear and tear, hypothermia, and infection. An initial noxious stimulus elicits an **inflammation of synovial membranes** that, in turn, leads to release of antigens through which the inflammatory process is maintained.

The antigen is taken up by synovial antigen-presenting cells; lymphocytes, including T-helper cells (p. 304), are activated and start to proliferate. In the process of interaction between lymphocytes and macrophages, the intensity of inflammation increases. Macrophages release proinflammatory messengers; among these, interleukin-1 and tumor necrosis factor α (TNFα) are important. TNFα is able to elicit a variety of proinflammatory actions (▶ Fig. 44.4**B**) that benefit defense against infectious pathogens but are detrimental in rheumatoid arthritis. The cytokines stimulate gene expression for COX-2; inflammation-promoting prostanoids are produced. The inflammatory reaction increases the activity of lymphocytes and macrophages, initiating a vicious circle. Synovial fibroblasts proliferate and release destructive enzymes; the inflamed characteristic pannus tissue develops and destructively invades joint cartilage and subjacent bone. Ultimately, ankylosis (loss of joint motion or bone fusion) with connective tissue scar formation occurs. Concomitant extra-articular disease may be superimposed. The disease process is associated with severe pain and restriction of mobility.

▶ **Pharmacotherapy.** Acute relief of inflammatory symptoms can be achieved by **prostaglandin synthase inhibitors** (p. 202; e.g., nonselective COX inhibitors or COX-2 inhibitors) and by **glucocorticoids.** The inevitably chronic use of both groups of substances is likely to cause significant adverse effects. Neither can halt the progressive destruction of joints.

Substances that are able to reduce the requirement for nonsteroidal anti-inflammatory drugs and to slow disease progression are labeled **disease-modifying agents.** Early use of these drugs is recommended. Their effect develops only after treatment for several weeks. Proliferation of lymphocytes can be slowed by **methotrexate** (p. 298) and **leflunomide,** which reduces the availability of pyrimidine nucleotides in lymphocytes (via inhibition of dihydroorotate dehydrogenase). For abatacept and ciclosporin, see p. 304. In addition, use is made of immunosuppressants such as **azathioprine** and **cyclophosphamide.** Intralysosomal accumulation and impaired phagocytic function may be involved in the action of chloroquine or **hydroxychloroquine,** as well as **gold compounds** (i.m.: aurothioglucose or aurothiomalate; oral: auranofin, less effective). The antibodies **infliximab, adalimumab, certolizumab,** and **golimumab** as well as the fusion protein **etanercept** intercept TNFα molecules, preventing them from interacting with membrane receptors of target cells. **Anakinra** is a recombinant analogue of the endogenous interleukin-1 antagonist. **Abatacept** imitates a physiological protein released by lymphocytes to terminate antigen presentation. **Tocilizumab** inactivates interleukin-6. The mechanisms of action of D-penicillamine and sulfasalazine are unknown. These drugs possess considerable potential for adverse effects. **Sulfasalazine** and **methotrexate** exhibit a relatively favorable risk–benefit ratio. Combination of disease-modifying drugs is possible.

Surgical removal of the inflamed synovial membrane (synovectomy) or radiotherapy by means of intra-articular injection of a radioisotope frequently provides long-term relief. If feasible, this approach is preferred because all pharmacotherapeutic measures entail significant adverse effects.

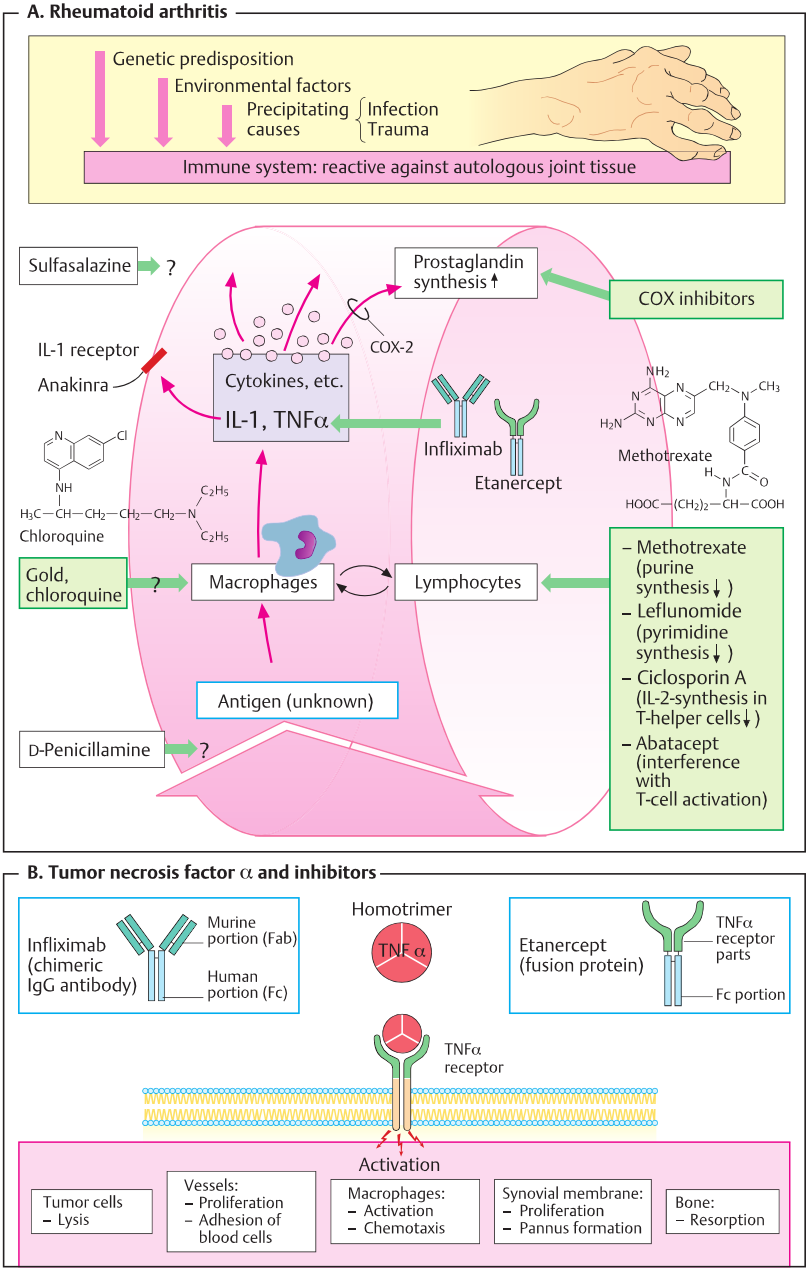

A. Rheumatoid arthritis
Genetic predisposition
Environmental factors
Precipitating causes
Infection
Trauma
Immune system: reactive against autologous joint tissue
Sulfasalazine
?
Prostaglandin synthesis
COX inhibitors
IL-1 receptor
Anakinra
COX-2
Cytokines, etc.
IL-1, TNFα
Infliximab
Etanercept
Methotrexate
Chloroquine
Gold, chloroquine
?
Macrophages
Lymphocytes
– Methotrexate (purine synthesis ↓)
– Leflunomide (pyrimidine synthesis ↓)
– Ciclosporin A (IL-2-synthesis in T-helper cells ↓)
– Abatacept (interference with T-cell activation)
Antigen (unknown)
D-Penicillamine
?
B. Tumor necrosis factor α and inhibitors
Infliximab (chimeric IgG antibody)
Murine portion (Fab)
Human portion (Fc)
Homotrimer
TNF α
Etanercept (fusion protein)
TNFα receptor parts
Fc portion
TNFα receptor
Activation
Tumor cells
– Lysis
Vessels:
– Proliferation
– Adhesion of blood cells
Macrophages:
– Activation
– Chemotaxis
Synovial membrane:
– Proliferation
– Pannus formation
Bone:
– Resorption

Fig. 44.4

Chronic Inflammatory Bowel Disease

Crohn disease (terminal ileitis) and **ulcerative colitis** are chronic, episodic bowel diseases associated with diarrhea. Patients are very unwell and serious complications may occur. As understood today, these diseases are due to a disorder of the bowel mucosal defense against intestinal bacteria. There is probably a genetic predisposition.

The human gut is colonized by 15 000 to 35 000 different types of microorganisms. On the one hand, the relationship is symbiotic; that is, the host organism provides the bacteria with living space and in turn is protected by the physiological bowel flora against pathogenic germs. This flora also makes certain nutrients available. On the other hand, the microorganisms are still aggressive and must be prevented from penetrating the bowel wall by the **mucosal barrier.**

The outermost layer of this barrier is a layer of mucus. Into this are secreted *defensins,* part of the innate immune response with an antibiotic action, and *IgA antibodies* (acquired specific immune response). Bowel epithelial cells are bound closely together by tight junctions. Bacterial antigens—for example, flagellin from the bacterial flagellum—can be recognized by bowel epithelial cells by means of *toll-like receptors* (TLR, innate immunity) located in the cell membrane. Antigens such as bacterial wall muramyldipeptides that reach the cytosol can be detected by *NOD-like receptors* (NLR, innate immunity). The epithelial cells defend themselves by increasing defensin production and secreting chemokines to obtain the assistance of neutrophil granulocytes. The immune system also monitors the situation on the other side of the mucosal barrier. *Dendritic cells,* which are part of the macrophage series, take up antigen using the processes that they extend into the lumen. M *cells* incorporated in the epithelium pass bacteria to macrophages underneath. The collected antigens are presented in lymphatic tissue, which involves the specific immune system in the form of T-helper lymphocytes and B cells. However, if an immune reaction becomes too great, inflammatory messengers such as tumor necrosis factor alpha (TNFα) can cause the epithelial cells to reduce the tightness of the tight junctions so that extracellular fluid passes into the bowel lumen, resulting in diarrhea.

The inflammatory reaction underlying chronic inflammatory bowel disease is as yet unclear. Possible factors in pathogenesis include unfavorable composition of bowel flora, disturbed epithelial barrier, and a hyperreactive immune system. There are so many differences between *Crohn disease* and *ulcerative colitis* that a common origin of these two diseases is unlikely (**C**).

However, the therapeutic approaches are very similar. The mode of action of **mesalazine**, i.e., the active constituent of sulfasalazine (p. 272) is unclear. Probiotic bacteria such as ***E. coli* Nissle** help avoid recurrence in ulcerative colitis. Antibiotics such as metronidazole (p. 274), which is effective against anaerobes, can be employed in severe cases. Various immunosuppressant drugs are also used. **Glucocorticoids** like *budesonide* (p. 244) achieve a high concentration on the mucosa following administration orally or by enema but have little systemic activity because of presystemic elimination in the liver. They can therefore be regarded as local therapy. **Immunosuppressants** such as *azathioprine* and *methotrexate* (p. 298) are given systemically, as are **infliximab** (p. 360), which inactivates TNFα, and **natalizumab** (p. 364), which inhibits leukocyte migration. The latter was approved in the USA for the treatment of Crohn disease. Additional measures employed in Crohn disease are *replacement* of fat-soluble vitamins and vitamin B_{12}), *cholestyramine* (p. 172) for diarrhea due to inadequate bile acid reabsorption in the ileum, along with *dietary measures.*

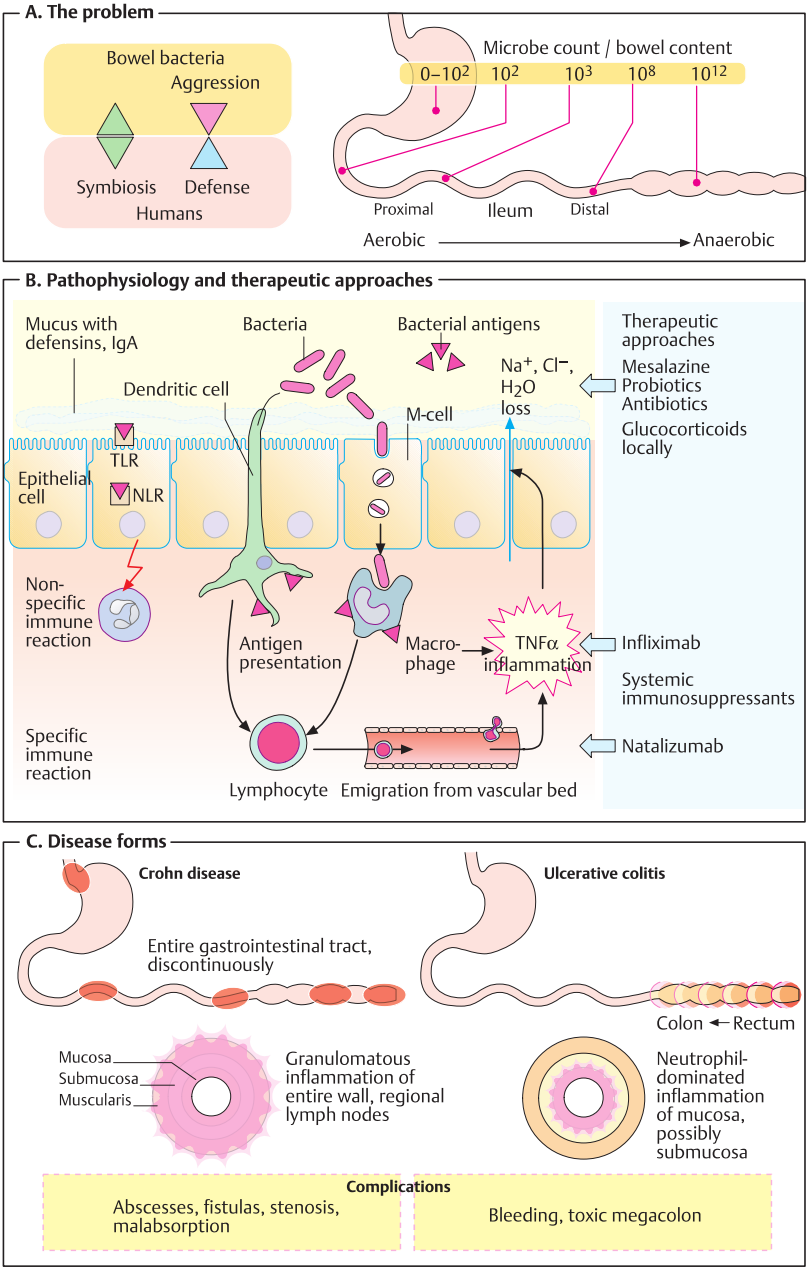

A. The problem
Bowel bacteria
Aggression
Symbiosis
Defense
Humans
Microbe count / bowel content
0–10²
10²
10³
10⁸
10¹²
Proximal
Ileum
Distal
Aerobic
Anaerobic
B. Pathophysiology and therapeutic approaches
Mucus with defensins, IgA
Bacteria
Bacterial antigens
Dendritic cell
M-cell
Na⁺, Cl⁻, H₂O loss
TLR
NLR
Epithelial cell
Non-specific immune reaction
Antigen presentation
Macro-phage
TNFα inflammation
Specific immune reaction
Lymphocyte
Emigration from vascular bed
Therapeutic approaches
Mesalazine
Probiotics
Antibiotics
Glucocorticoids locally
Infliximab
Systemic immunosuppressants
Natalizumab
C. Disease forms
Crohn disease
Entire gastrointestinal tract, discontinuously
Ulcerative colitis
Colon ← Rectum
Mucosa
Submucosa
Muscularis
Granulomatous inflammation of entire wall, regional lymph nodes
Neutrophil-dominated inflammation of mucosa, possibly submucosa
Complications
Abscesses, fistulas, stenosis, malabsorption
Bleeding, toxic megacolon

Fig. 44.5

Multiple Sclerosis

► **Pathophysiology.** In an autoimmune process, T-helper lymphocytes attack foci of oligodendrocytes in the brain and spinal cord. As a result of destruction of their myelin sheaths, axons cease to function or are even lost. The clinical symptoms depend on the location of the foci. The inflammation can subside, and repair processes get underway, with the production of replacement oligodendrocytes and a glial scar. In this way, the symptoms improve in the relapsing remitting form of the disease. Over the years, however, this can change into a chronic progressive form.

► **Treatment.** **In the acute episode** glucocorticoids in very high doses are given intravenously for 3–5 days. Glucocorticoids (p. 242) have broad and intensive anti-inflammatory activity. They are well tolerated when used in the short term.

Continuous therapy is used for **prevention of relapses** (► Fig. 44.6A). This includes:

- *Disease-modifying drugs:* glatiramer acetate, β-interferon (INF-β), azathioprine
- *Escalation agents,* when disease-modifying drugs do not suffice: natalizumab, mitoxantrone, fingolimod.

In ► Fig. 44.6A the therapeutic agents are classified according to the pathophysiological process.

► **Inhibition of lymphocyte activation.** Peripheral lymphocytes, especially T-helper cells, directed against components of myelin sheaths in the CNS are activated for an as yet unknown reason. Glatiramer acetate consists of synthetic peptides polymerized in random order from the amino acids glutamic acid, lysine, alanine, and tyrosine. Glatiramer resembles the basic myelin protein of oligodendrocytes. It appears to work as a "molecular decoy" to block the myelin protein receptors of the lymphocytes, thereby blocking their activation. In addition, it apparently promotes the restricting activity of regulatory T-helper cells.

► **Inhibition of lymphocyte multiplication.** Proliferation of lymphocytes forms the basis of an acquired immune response. This is inhibited by *mitoxantrone,* a DNA-intercalating cytostatic antibiotic (p. 298) with an additional inhibitory effect on topoisomerase by *azathioprine* (p. 360), the precursor of a cytostatic antimetabolite, and by *teriflunomide,* the active metabolite of leflunomide (p. 360).

► **Inhibition of lymphocyte release into the circulation.** *Fingolimod* has an unusual mechanism of action on the sphingosine-1-phosphate (S1P) receptor, a G-protein-coupled receptor (GPCR). This normally mediates the release of lymphocytes from lymphatic tissue. Fingolimod is first activated to an S1P agonist by phosphorylation. In this form it induces a physiological "protective mechanism" in the cell against excessive activation by reuptake of the receptors into the interior of the cell. Fingolimod phosphate therefore disables the receptor.

► **Inhibition of passage of lymphocytes into the CNS.** *Natalizumab* is a humanized antibody against the alpha-4 subunit of integrins. Passage of leukocytes from the blood into the tissue involves a number of steps. *Margination:* blood flow is slowed by inflammatory vasodilation and the lymphocytes come close to the endothelium. *Adhesion:* adhesive bridges develop between leukocytes and endothelium. Initially, *selectins* and *selectin ligands* come in contact and slow down the *"leukocyte rolling"* on the endothelium. *Integrins* in the leukocytes then form stable bridges with endothelial adhesion proteins (ICAM: intercellular adhesion molecule; VCAM: vascular cell adhesion molecule). This is prevented by natalizumab so the lymphocytes cannot migrate.

Progressive multifocal leukoencephalopathy (PML) is a rare but extremely dangerous side effect. This is due to disinhibition of the JC virus (J.C. were the initials of the patient in whom the virus was first isolated). This virus is widespread but is normally held in check by the immune system. Natalizumab must not be given together with other immunosuppressant drugs. It is intended only for monotherapy.

Little is known about the mechanism of action of **interferon β**, an effective immune modulator.

The same applies for the orally administered **dimethylfumarate**; perhaps it acts through a GPCR of hydroxycarbonic acid receptor type.

Symptomatic measures are used to manage the *consequences of axon damage* (spasticity, pain, bladder voiding disorders, etc.).

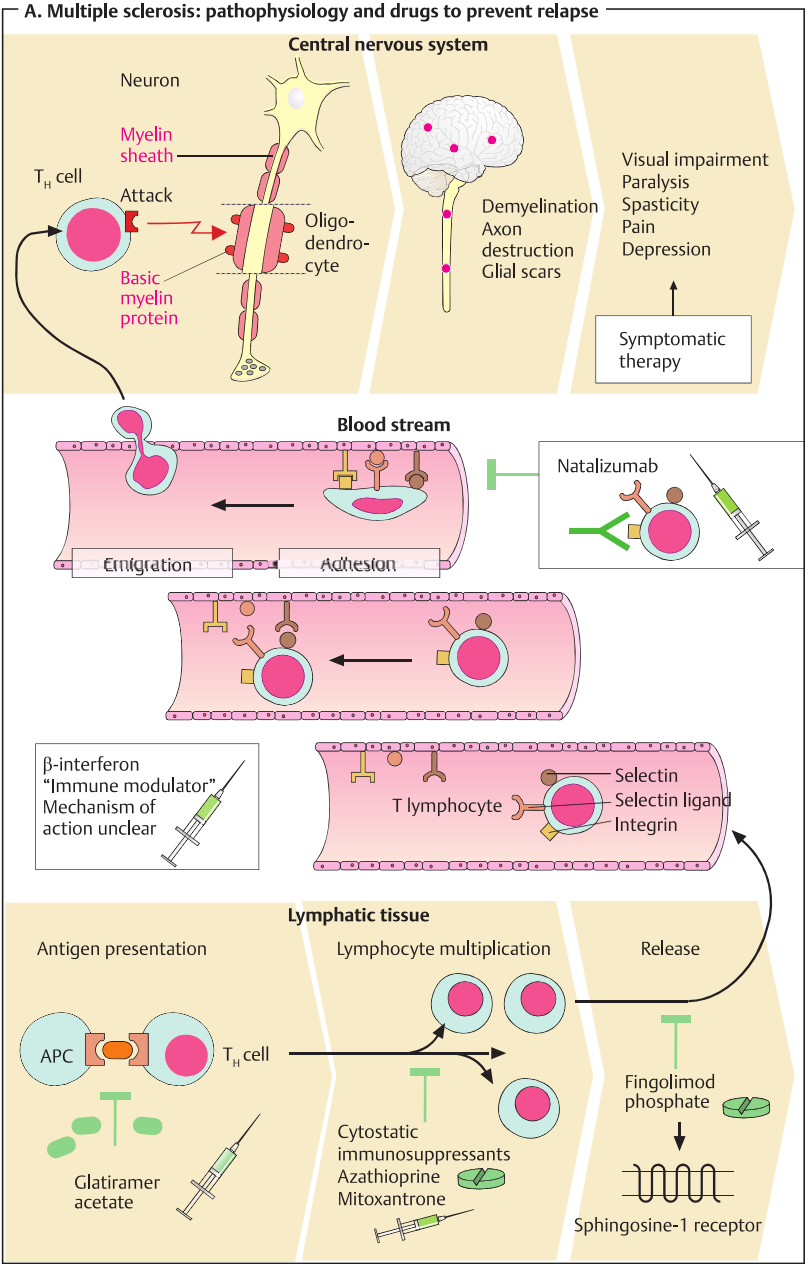

A. Multiple sclerosis: pathophysiology and drugs to prevent relapse
Central nervous system
Neuron
Myelin sheath
T_H cell
Attack
Oligo-dendro-cyte
Basic myelin protein
Demyelination
Axon destruction
Glial scars
Visual impairment
Paralysis
Spasticity
Pain
Depression
Symptomatic therapy
Blood stream
Natalizumab
Emigration
Adhesion
β-interferon
"Immune modulator"
Mechanism of action unclear
T lymphocyte
Selectin
Selectin ligand
Integrin
Lymphatic tissue
Antigen presentation
Lymphocyte multiplication
Release
APC
T_H cell
Glatiramer acetate
Cytostatic immunosuppressants
Azathioprine
Mitoxantrone
Fingolimod phosphate
Sphingosine-1 receptor

Fig. 44.6

Further Reading

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Glossary

Glossary

7-TM receptor	Receptor with 7 transmembrane helices; another and more accurate name for "G protein-coupled receptor," which reflects the fact that such receptors can also produce effects without the involvement of G proteins
ABC transporter	Transport proteins containing an ATP-binding cassette
Absorption	Passage of a substance from an external or internal surface into the underlying tissue; as a result of → presystemic elimination the amount of absorbed substance can be greater than the systemically available amount
Absorption rate	Absorbed quantity of a substance divided by the amount of the substance available for absorption (see → Availability, pharmaceutical)
Accumulation	Gradual increase in the drug concentration in the body when administered at regular intervals, when less substance is eliminated than administered in the dosing intervals until → Cumulative equilibrium is reached
Activity, intrinsic	Ability of a → Ligand to trigger receptor stimulation
Addiction	Uncontrollable desire for repeated use of a substance that produces a (possibly ecstatic) state of well-being; typically associated with → Habituation so that absence of it leads to psychological and physical withdrawal symptoms; everything else is subordinated to procuring the substance
ADE	Adverse drug effect
Aerosol	Preparation containing extremely fine solid or liquid particles in a gas
Affinity	Tendency of a substance to bind to a site (e.g., receptor protein, albumin); expressed as the reciprocal of the substance concentration for half-maximum binding, cf. → K_D value
Agonist	Substance with affinity for a receptor and → Intrinsic activity to stimulate it
Agonist, inverse	Substance with affinity for a receptor, which may be able to switch off any spontaneous basal activity of the receptor protein, and which therefore has (negative) intrinsic activity opposite to that of the agonist
Agonist, partial	Agonist with intrinsic activity lower than the maximum possible activity of a "full agonist", can also act as → Partial antagonist
Alkaloid	Basic constituent of plants
Allosteric binding site	Binding site of a substance located on a target protein (receptor, enzyme, transport protein) outside the (orthosteric) binding site for the physiologic "principal ligand" (e.g., benzodiazepine binding site on the $GABA_A$ receptor, NO binding site on soluble guanylate cyclase)
Allosteric interaction	Substance binding to an → Allosteric binding site, usually with the aim of influencing an (orthosteric) "principal ligand"
Amphiphilic	Solubility property of a substance, characterized by the spatial proximity of a hydrophilic and a lipophilic part of the molecule so that the substance is not readily fat- or water-soluble but preferably occupies an intermediate layer between a polar and nonpolar milieu
Analogue substance	Drug that is the same pharmacologically though chemically altered compared with the first representative of a drug class
Antagonism, allosteric	Inhibition of binding and/or the effect of an agonist at the "principal binding site" of a receptor as a result of a substance acting on an → Allosteric binding site
Antagonism, competitive	Inhibition of binding and the effect of a receptor agonist by means of an → Antagonist, which competes with the agonist for binding at the same receptor site; the maximum agonist effect can be regained by increasing the agonist concentration
Antagonism, functional	Inhibition of the effect of an agonist–receptor interaction by causing an opposite biological reaction through a different receptor
Antagonism, noncompetitive	Inhibition of binding and the effect of a receptor agonist by means of an → Antagonist, the inhibitory effect of which cannot be fully compensated by increasing the agonist concentration, e.g., when the receptors are irreversibly occupied

Antagonist	Substance with → Affinity for a receptor, which counteracts the effect of an → Agonist ("anti-agonist")
Antagonist, neutral	Antagonist that does not influence the spontaneous basal activity of the receptor protein when it binds to the receptor, that is, it has no (positive or negative) intrinsic activity
Antagonist, partial	Antagonist with partial (submaximal) intrinsic activity – thus preventing the greater effect of the full agonist, replacing it with its own lesser effect. Partial antagonist is therefore essentially synonymous with partial agonist
Antidote	A remedy to counteract a poison
Availability, pharmaceutical	Proportion of the substance contained in a pharmaceutical form (e.g., tablet) that is released and available for absorption
Availability, systemic	→ Bioavailability
Bateman function	Mathematical description of the time course of the concentration of active substance in the plasma which results when a drug is absorbed into a uniform distribution space and eliminated from this at a certain rate.
Bioavailability	Degree of availability of an administered drug (at the site of administration and/or in the plasma: measurable after oral administration as the ratio of the areas under the plasma concentration/time curves after oral and intravenous administration.
Bioequivalence	Is present between a → Copy and the original drug preparation when the → Bioavailability of the drug from the copy corresponds to that of the original preparation with regard to quantity and time course of release of the active substance
Biotransformation	Chemical transformation of a substance in the body
Blood–brain barrier	High barrier function of the blood vessels in the CNS based on the tight junctions between the endothelial cells without fenestrations; the cells contain "drug pumps" facing the circulation side
Capsule	(Elastic) shell containing a medicine
Chirality	Mirror image–like "right- and left-handedness" of two molecules that cannot be superimposed (enantiomers)
Circumventricular organs	Brain regions without → Blood–brain barrier around the third and fourth cerebral ventricles, including the neurohypophysis and area postrema
Clearance	The volume of plasma cleared of the drug per unit time (e.g., mL/min)
Coated tablet	A drug within a core that is covered by a hard or soft shell
Combination preparation	Preparation with more than one active substance
Compliance	The degree to which a patient follows medical instructions
Controlled release	Time-dependent release of drug by manipulation of the structure of the formulation
Copy (imitator) product	Medicinal product containing the same drug as the initial provider's product, which may be marketed by another provider following expiry of the original product's patent, see also → Generic
Coupling reaction	Biotransformation reaction linking an endogenous molecule to a substance that is excreted to hasten its elimination (phase II reaction)
Cumulative equilibrium	Final → Accumulation, when the amount of active substance eliminated in the dosing interval is equal to the administered amount, on account of the concentration that has been reached
CYP (with indices)	Acronym for cytochrome oxidases, indices (e.g., CYP3A4) for the numerous isoenzymes, indicating the main family ("3"), the subfamily ("A") and the individual number ("4")
Dependency	Often used synonymously with → Addiction
Disintegration	Breaking up of a tablet, capsule etc. in the gastrointestinal tract
Dissolution	Dissolving of a drug in gastrointestinal juice
Distribution volume, apparent	Fictive pharmacokinetic parameter obtained when the amount of a drug in the body is divided by the concentration in the plasma (including plasma protein binding)

Dose–effect curve	Graphic representation of the quantitative dependence of an effect on the administered quantity of the drug
Dose-linear kinetics	see Kinetics, dose-linear
Drug	From the French "drogue" = dried herb. A substance intended for use in the treatment of disease. In its literal sense: dried plant (parts) possessing therapeutic properties, e.g., opium, colloquial: narcotic, also in relation to chemically pure and synthetic substances such as heroin.
Drug interaction	Usually unwanted reciprocal effect of drugs used together with regard to → Pharmacodynamics and → Pharmacokinetics
Efficacy	The ability of a drug to produce the desired effect
Elimination	Breakdown and/or excretion of a substance
EMA	European Medicines Agency
Enantiomer	One of the two mirror-image molecules of a → Racemate
Enantioselectivity	Preferred → Affinity of a binding structure (e.g., receptor, enzyme, transporter) for one of the two → Enantiomers of a → Racemate
Enterohepatic circulation	Circulation of a substance between the intestine and liver when it is absorbed from the intestine, eliminated from the liver in the bile and then reabsorbed from the intestine
Enzyme induction	Increase in cellular synthesis of → Biotransformation enzymes of the → CYP series produced by binding of certain substances to transcription factors
G-protein	Guanine nucleotide-binding protein
Generic	Medicinal product marketed under its International Drug Name with the addition of the pharmaceutical company name; the term is often also used for copycat products with invented names
GPCR	G-protein-coupled receptor
Habituation	Synonymous with "increased tolerance" or simply "tolerance": reduction in the physical and/or mental effect of a substance because of the body's counter-regulatory mechanisms; typically developing with chronic administration of the substance and leading to "withdrawal symptoms" if administration is interrupted, due to futile counter-regulation. Not synonymous with → Addiction, as an excessive rise in blood pressure after sudden discontinuation of an antihypertensive agent can be an expression of habituation, purely somatic in this instance
Half-life	The time required for the concentration of a drug to fall to half of the original level
Ion channel receptor	→ Ion channel, ligand-gated
Ion channel, ligand-gated	Ion channel protein, the activity of which is produced by a messenger
Ion channel, voltage-gated	Ion channel protein, the activity of which is controlled by the membrane potential
K_D value	Equilibrium dissociation constant of a binding reaction according to the law of mass action; corresponds to the concentration of substance for 50% occupation of receptors; $1/K_D$ is the affinity constant
Kinetics, dose-linear	Pharmacokinetic turnover rate (turnover per unit time), proportional to the concentration of the substance, for example, non-saturable glomerular filtration and enzymatic conversion in the nearly linear initial part of the Michaelis–Menten curve; in consequence, pharmacokinetic parameters of substances such as the half-life and clearance are usually dose-independent
Ligand	Substance molecule that docks on a binding site (receptor)
Lotion	A suspension of solid and insoluble components in water for application to the skin
Matrix tablet	Oral formulation with a drug embedded in a framework to delay its release
Medicinal product	Drug in a pharmaceutical form (e.g., tablet, suppository, injection solution) that can contain other substances (e.g., fillers, excipients, preservatives) as well as the drug. Acts physically on the body for the purpose of diagnosis or treatment

Me-too substance	An analogue substance that imitates the chemical structure of a successful pharmaceutical product, sold by competing pharmaceutical firms
MRP	Multidrug resistance protein
NNT	"Number needed to treat"; statistical measure: number of persons that must be treated to prevent a disease for one person to derive benefit
Partial agonist	→ Agonist, partial
Partial antagonist	→ Antagonist, partial
P-glycoprotein	Efflux pump belonging to the → ABC transporter family
Pharmaceutical form	Form of preparation of a medicinal product, e.g., solution, tablet, capsule etc.
Pharmacodynamics	The study of the biological effects of drugs (descriptive or explanatory)
Pharmacogenetics	The study of the influence of heredity on the effect of drugs
Pharmacokinetics	The study of the "fate" of drugs in the body
Pharmacovigilance	Measures aimed at reducing the risks of medicines during clinical trials and following marketing authorization
Placebo	A medicinal product that does not contain an active substance (dummy medicine) without somatic effect but often with a considerable psychological effect ("placebo effect")
Polymorphism of biotransformation	Interindividual difference in the capacity for biotransformation reactions due to genetic differences in the range of enzymes
Potency	Strength of effect; indicated by the drug concentration required for half-maximum effect
Preclinical trial	Pharmacological and toxicological studies performed before a potential medicine is tested in humans
Presystemic elimination	Inactivation of a drug between its absorption at the site of administration and its entry into the systemic circulation; possible especially in the liver and intestinal epithelium
Protein binding	Plasma protein binding: percentage of the total amount of the substance in the plasma that is bound to plasma proteins
Racemate	Mixture of equal parts of two mirror-image molecules that cannot be superimposed (enantiomers)
Receptor	Functional protein for converting the binding of a messenger (to the ligand-binding domain of the protein) into an effect (mediated through the receptor's signal transduction domain)
Receptor with kinase activity	Receptor located in the plasmalemma; extracellular binding of the messenger switches on tyrosine kinase activity in the intracellular domains
Receptor, G-protein-coupled	Receptor located in the plasmalemma with 7 transmembrane helices, extracellular messenger binding, intracellular G-protein contact
Receptor, transcription-regulating	Intracellular location, acts as a transcription factor to control gene expression following binding of the messenger
Route of administration	Administration of an active substance by the oral, rectal, inhaled, transdermal, intravenous route etc.
Scientific medicine	Unlike the scholastic and static medicine of the Middle Ages, which was submissive to received authority, scientific medicine is based on an anti-authoritarian and doubting way of thinking that allows medical progress by means of controlled experiments and clinical studies
Signal transduction	Biochemical chain of reactions from receptor stimulation to alteration of cell function
Suppository	A formulation for introduction into the rectum, vagina, or urethra
Technology, pharmaceutical	Study of the formulations used for medicinal products
Therapeutic index	Gap between the dosage required for treatment and the toxic dose
Tincture	Alcoholic extract of herbal constituents obtained by steeping plants or parts of plants in ethanol
Xenobiotic	Foreign substance

Drug Index

Table 47.1 Antibodies

Drug name	Trade name	Target structure	Comment	Indication
Antibodies against neoplasms				
Alemtuzumab	MabCampath®	CD52 (lymphocytes, monocytes)		Chronic lymphocytic leukemia
Bevacizumab	Avastin®	VEGF		Colon, rectum, breast cancer, and others
Brentuximab vedotin	Adcetris®	CD30	Linked cytostatic (monomethyl auristatin E → tubulin) is delivered to its target	Hodgkin lymphoma
Catumaxomab	Removab® intraperitoneal infusion	EpCAM (carcinoma) and CD3 (lymphocyte)	Believed to transport lymphocytes to carcinoma cells	Malignant ascites
Cetuximab	Erbitux®	HER1 (EGFR, epidermal growth factor receptor)		Colorectal carcinoma
90Y ibritumomab tiuxetan	Zevalin®	CD20 (B- lymphocytes)	Radioactive isotope on the Fc fragment is delivered to its target by the AB	Follicular non-Hodgkin lymphoma
Ipilimumab	Yervoy®	CTLA-4, cytotoxic T-lymphocyte antigen 4	Inhibition of CTLA-4-induced inhibition of antigen presentation → increased T-cell activation	Malignant melanoma
Obinutuzumab	Gazyvaro®	CD20 (B-lymphocytes)		Chronic lymphocytic leukemia
Ofatumumab	Arzerra®	CD20 (B-lymphocytes)		Chronic lymphocytic leukemia
Panitumumab	Vectibix®	HER1		Colon cancer
Pertuzumab	Perjeta®	Inhibition of HER2 dimerization		Breast cancer
Rituximab	MabThera®	CD20 (B-lymphocytes)		Follicular lymphoma
Siltuximab	Sylvant®	Interleukin 6, (IL-6)	Enlargement of multiple lymph nodes	Multicentric Castleman disease
Trastuzumab	Herceptin®	HER2		Breast cancer
Trastuzumab emtansine	Kadcyla®	HER2	Antibody-cytotoxic maytansine conjugate	Breast cancer
Antibodies against harmful inflammation				
Abatacept	Orencia®	CD86 on antigen-presenting cells	Human AB Fc fragment fused with CTLA-4, a "CD86 lid"	Rheumatoid arthritis
Aflibercept	Eylea®	VEGF	VEGF receptor/IgG Fc fragment	Wet form of macular degeneration
Adalimumab	Humira®	Tumor necrosis factor α (TNFα)	Human AB	Rheumatoid arthritis
Basiliximab	Simulect®	IL-2 receptor on lymphocytes	Chimeric mouse-human AB	Prevention of transplant rejection
Belatacept	Nulojix®	CD86 on antigen-presenting cells	Human AB Fc fragment fused with CTLA-4, a "CD86 lid"	Immunosuppression after kidney transplant

Table 47.1 continued

Drug name	Trade name	Target structure	Comment	Indication
Belimumab	Benlysta®	BLyS, belonging to the TNF superfamily, stimulates B-lymphocytes to produce antibodies	Human AB against B-lymphocytes stimulator BLyS	Systemic lupus erythematosus
Canakinumab	Ilaris®	Interleukin-1 β	Genetically determined overproduction of IL-1 β with excessive tendency to inflammation	CAPS syndrome = cryopyrin-associated periodic syndromes
Certolizumab pegol	Cimzia®	Tumor necrosis factor α (TNFα)	Antibody without Fc fragment to avoid Fc-mediated immune processes	Rheumatoid arthritis
Denosumab	Prolia®	RANKL on osteoblasts	Inhibition of osteoblast-mediated osteoclast activation	Osteoporosis
Eculizumab	Soliris®	Complement factor 5	Interruption of the complement cascade on erythrocytes to protect against hemolysis	Paroxysmal nocturnal hemoglobinuria
Etanercept	Enbrel®	Tumor necrosis factor α (TNFα)	TNFα receptor fused with human AB Fc fragment	Rheumatoid arthritis
Golimumab	Simponi®	Tumor necrosis factor α (TNFα)	Long duration of action of 1 month	Rheumatoid arthritis, psoriatic arthritis, etc.
Infliximab	Remicade®	Tumor necrosis factor α (TNFα)	Human-murine (Fc-Fab) AB	Crohn disease, ulcerative colitis, rheumatoid arthritis, etc.
Muromonab CD3	Orthoclone®	CD3 receptor of T-lymphocytes	Murine AB	Immunosuppression to prevent transplant rejection
Natalizumab	Tysabri®	Leukocyte integrin α4β1	Humanized AB	Multiple sclerosis
Tocilizumab	RoActemra®	IL-6 receptor	Humanized AB	Rheumatoid arthritis
Ustekinumab	Stelara®	IL-12 und IL-23	Humanized AB	Plaque psoriasis
Vedolizumab	Entyvio®	Lymphocyte integrin α4β7	Humanized AB	Ulcerative colitis, Crohn disease

Table 47.2 Kinase inhibitors (without antibodies to receptor tyrosine kinases)

Drug name	Trade name	Target structure	Indication
Receptor tyrosine kinases			
Afatinib	Giotrif® tablet	EGFR	Non–small cell lung cancer
Axitinib	Inlyta® tablet	VEGF receptor-1,-2,-3	Renal cell carcinoma (reserve)
Cabozantinib	Cometriq® capsule	Various receptor tyrosine kinases	Medullary C-cell thyroid cancer
Crizotinib	Xalkori® capsule	ALK (anaplastic lymphoma kinase)	ALK-positive non–small cell lung cancer
Erlotinib	Tarceva® tablet	HER1 (EGFR) tyrosine kinase	Non–small cell lung cancer
Gefitinib	Iressa® tablet	EGFR mutants with overactive tyrosine kinase	Non–small cell lung cancer
Lapatinib	Tyverb® tablet	HER2	Breast cancer (reserve)
Pazopanib	Votrient® tablet	Various receptor tyrosine kinases	Renal cell carcinoma
Sunitinib	Sutent® capsule	Various receptor tyrosine kinases	GIST, renal cell carcinoma; reserve in each case
Vandetanib	Caprelsa® tablet	Various receptor tyrosine kinases: VEGF2, RET, EGF receptor	Medullary C-cell thyroid cancer
Intracellular tyrosine kinases			
Bosutinib	Bosulif® tablet	BCR-Abl tyrosine kinase	Chronic myeloid leukemia, 2nd choice after imatinib, nilotinib, dasatinib
Dasatinib	Sprycel® tablet	BCR-Abl	e.g., chronic myeloid leukemia (reserve)
Imatinib	Glivec® tablet	BCR-Abl	e.g., chronic myeloid leukemia
Nilotinib	Tasigna® capsule	BCR-Abl	e.g., chronic myeloid leukemia (reserve)
Ponatinib	Iclusig® tablet	BCR-Abl tyrosine kinase	Chronic myeloid leukemia, 2nd choice after imatinib, nilotinib, dasatinib
Ruxolitinib	Jakavi® tablet	Janus kinases 1,2, receptor-associated intracellular tyrosine kinases for STAT (signal transducer and activator of transcription)	Myelofibrosis
Intracellular serine/threonine kinases and other kinases			
Dabrafenib	Tafinlar® capsule	BRAF V600 mutant	Melanoma
Sorafenib	Nexavar® tablet	Intracellular tyrosine and serine/threonine kinases, receptor tyrosine kinases	Advanced renal cell carcinoma
Vemurafenib	Zelboraf® tablet	BRAF V600 mutant (a serine/threonine kinase)	Advanced melanoma
"Multikinase" inhibitors			
Regorafenib	Stivarga® tablet	Various membrane-bound and intracellular kinases	Metastatic colorectal carcinoma

Table 47.3 Drug names → trade names

Drug Name	Trade Name
A	
Abacavir	Ziagen®
Abarelix	Plenaxis®
Abatacept	Orencia®
Abciximab	ReoPro®
Acamprosate	Campral®
Acarbose	Glucobay®, Precose®
Acebutolol	Sectral®
Acenocoumarin (= nicoumalone)	Sinthrome®
Acetaminophen (= paracetamol)	Anadin®, Genapap®, Panadol®, Tylenol®, Valorin®
Acetazolamide	Diamox®
Acetylcysteine	Fluimucil®, Mucomyst®, Parvolex®
Acetyldigoxin	Novodigal®
Acetylsalicylic acid	Angettes®, Aspirin®, Bufferin®, Caprin®, Ecotrin®, Genacote®
Aciclovir	Zovirax®
Acipimox	Olbetam®
Acitretin	Neotigason®, Soriatane®
Adalimumab	Humira®
Adefovir	Hepsera®
Albuterol see Salbutamol	Proventil®, Ventolin®
Alcuronium	Alloferin®
Aldosterone	Aldocorten®
Alendronate	Fosamax®
Alfentanil	Alfenta®, Rapifen®
Alfuzosin	UroXatral®, Xatral®
Aliskiren	Rasilez®, Tekturna®
Allethrin	Bioallethrin®
Allopurinol	Zyloprim®, Zyloric®
Alprazolam	Xanax®
Alprenolol	Apllobal®, Aptine®, Gubernal®
Alprostadil	Caverject®, Edex®, Muse®, Viridal®
Alteplase	Actilyse®, Activase®
Aluminum hydroxide	Aldrox®, Alternagel®, Dermagran®
Amantadine	Lysovir®, Symmetrel®
Amikacin	Amikin®
Amiloride	Midamor®
Amiloride + hydrochlorothiazide	Moduret®, Navispare®
Aminomethylbenzoic acid	Pamba®
Aminophylline	Phyllocontin®

Drug Name	Trade Name
Amiodarone	Cordarone®
Amitriptyline	Elavil®, Endep®, Tryptizol®
Amitriptyline + perphenazine	Triptafen®
Amlodipine	Istin®
	Norvasc®
Amorolfine	Loceryl®
Amoxicillin	Amoxil®, Trimox®
Amoxicillin + clavulanic acid	Augmentin®
Amphotericin B	Abelcet®, Ambisone®, Amphocin®, Amphotec®, Fungilin®, Fungizone®
Ampicillin	Omnipen®, Penbritin®, Principen®
Ampicillin + sulbactam	Unasyn®
Amprenavir	Agenerase®
Amrinone	Inocor®
Anakinra	Kineret®
Anastrozole	Arimidex®
Angiotensin amide	Hypertensin®
Anidulafungin	Ecalta®, Eraxis®
Anistreplase	Eminase®
Apomorphine	Apo-go®, Apokyn®
Apraclonidine	Iopidine®
Aprepitant	Emend®
Aprindine	Fiboran®
Ardeparin	Normiflo®
Argatroban	Argata®
Aripiprazole	Abilify®
Artemether + lumefantrine	Riamet®
Artesunate	Arsumax®, Falcigo®, Plasmotrim®
Articaine	Ultracain®
Asparaginase (= crisantaspase)	Elspar®
Aspirin	Disprin®, Nu-Seals®
Astemizole	Hismanal®
Atenolol	Tenormin®
Atomoxetine	Strattera®
Atorvastatin	Lipitor®
Atosiban	Tractocile®
Atovaquone	Mepron®, Wellvone®
Atovaquone + proguanil	Malarone®
Atracurium	Tracrium®
Atropine	Atropen®
Auranofin	Ridaura®

Table 47.3 Drug names → trade names (cont.)

Drug Name	Trade Name
Aurothioglucose	Solganal®
Aurothiomalate sodium	Myocrisin®
Azapropazone	Rheumox®
Azathioprine	Imuran®
Azithromycin	Zithromax®
Azlocillin	Securopen®
Aztreonam	Azactam®
B	
Bacitracin + neomycin	Aktracin®, Baciguent®
Bacitracin + neomycin + polymyxin B	Neosporin®
Baclofen	Lioresal®
Bamipine	Soventol®
Basiliximab	Simulect®
Beclomethasone	Aerobec®, Beclazone®, Becloforte®, Becodisks®, Beconase®, Becotide®, Qvar®
Bedaquiline	Sirturo®
Befunolol	Glauconex®
Benazepril	Lotensin®
Benzocaine	Americaine®, Anbesol®, Orajel®
Benztropine/benzatropine	Cogentin®
Benzyl benzoate	Ascabiol®
Betaxolol	Betoptic®, Kerlone®
Bevacizumab	Avastin®
Bezafibrate	Bezalip®
Bicalutamide	Casodex®
Bimatoprost	Ganfort®, Lumigan®
Biperiden	Akineton®
Bisacodyl	Dulcolax®
Bismuth subsalicylate	Pepto-Bismol®
Bisoprolol	Cardicor®, Emcor®, Zebeta®
Bitolterol	Tornalate®
Bivalirudin	Angiomax®, Angiox®
Bleomycin	Blenoxane®
Bortezomib	Velcade®
Bosentan	Tracleer®
Botulinum toxin type A	Botox®, Dysport®, Oculinum®
Botulinum toxin type B	Myobloc®, NeuroBloc®
Brimonidine	Alphagan®
Brinzolamide	Azopt®
Bromazepam	Lexotan®
Bromhexine	Bisolvon®
Bromocriptine	Parlodel®
Brotizolam	Lendormin®
Budesonide	Entocort EC®, Pulmicort®, Rhinocort®
Budipine	Parkinsan®
Bumetanide	Bumex®, Burinex®
Bunitrolol	Stresson®
Buprenorphine	BuTrans®, Subutex®, Temgesic®
Bupropion	Wellbutrin®, Zyban®
Buserelin	Suprecur®, Suprefact®
Buspirone	Buspar®
Busulfan	Busilvex®, Myleran®
Butylscopolamine	Buscopan®
C	
Cabergoline	Dostinex®
Calcifediol (= vitamin D)	Dedrogyl®
Calcitonin	Calcimar®, Miacalcin®
Calcitriol	Rocaltrol®
Calcium carbonate	Calchichew®, Caltrate®
Camazepam	Albego®
Canagliflozin	Invokana®
Candesartan	Atacand®
Canrenone	Soldactone®, Venactone®
Capecitabine	Xeloda®
Capreomycin	Capastat®
Captopril	Capoten®
Carazolol	Suacron®
Carbachol	Isopto®, Miostat®
Carbamazepine	Tegretol®
Carbenicillin	Geocillin®
Carbetocin	Pabal®
Carbidopa	Lodosyn®
Carbimazole	Neo-Mercazole®
Carboplatin	Paraplatin®
Carteolol	Ocupress®
Carvedilol	Coreg®
Caspofungin	Cancidas®
Cefaclor	Distaclor®
Cefalexin	Ceporex®, Keflex®
Cefotaxime	Claforan®
Ceftazidime	Fortum®
Ceftriaxone	Rocephin®
Celecoxib = colecoxib	Celebrex®
Celiprolol	Selectol®
Cellulose	Avicel®
Certoparin	Embolex®

Table 47.3 Drug names → trade names (cont.)

Drug Name	Trade Name
Cetirizine	Zirtek®
Cetrorelix	Cetrotide®
Cetuximab	Erbitux®
Chloral hydrate	Welldorm®, Noctec®
Chlorambucil	Leukeran®
Chloramphenicol	Chloromycetin®, Kemicetine®
Chlordiazepoxide	Librium®
Chlormadinone	Gestafortin®
Chloroprocaine	Nesacaine®
Chloroquine	Avloclor®, Nivaquine®
Chlorpromazine	Largactil®, Thorazine®
Chlorthalidone	Hygroton®
Cholestyramine	Prevalite®, Questran®
Chorionic gonadotropin (HCG)	Choragon®, Ovitrelle®, Pregnyl®
Ciclosporin (= cyclosporin A)	Neoral®, Sandimmune®
Cilazapril	Vascace®
Cilostazol	Pletal®
Cimetidine	Dyspamet®, Tagamet®
Cinacalcet	Mimpara®
Ciprofloxacin	Ciloxan®, Cipro®, Ciproxin®, Truoxin®
Cisapride	Propulsid®
Cisplatin	Platinol®
Citalopram	Celexa®, Cipramil®
Cladribine	Leustatin®, Litak®
Clarithromycin	Biaxin®, Klacid®
Clemastine	Tavegil®, Tavist®
Clindamycin	Cleocin®, Dalacin®
Clodronate	Bonefos®
Clofazimine	Lamprene®
Clofibrate	Atromid-S®
Clomethiazole	Heminevrin®
Clomiphene	Clomid®
Clonazepam	Klonopin®, Rivotril®
Clonidine	Catapres®, Dixarit®
Clopidogrel	Iscover®, Plavix®
Clorazepate	Tranxene®
Clotrimazole	Canesten®, Gyne-Lotrimin®, Mycelex®
Clozapine	Clozaril®, Denzapine®, Zaponex®
Codeine (in combinations)	Codinex®, Robitussin®
Colchicine	Colcrys®
Colesevelam	Cholestagel®, Welchol®
Colestipol	Colestid®
Colistin	Colomycin®, Promixin®
Corticotropin	Acthar®, Synacthen®
Cortisone	Cortone®
Cotrimoxazole	Bactrim®, Septrin®
Cromoglicate (= cromolyn)	Intal®, Nasalcrom®, Opticrom®, Rynacrom®, Vividrin®
Cyanocobalamin (Vit. B_{12})	Nascobal®, Cytamen®, Neo-Cytamen®
Cyclofenil	Ondogyne®, Sexovid®
Cyclophosphamide	Endoxana®
Cycloserine	Seromycin®
Cyproterone acetate	Androcur®, Cyprostat®
Cytarabine	Cytosar-U®, Depocyte®
D	
Dabigatran	Pradaxa®
Dacarbazine	Dtic-Dome®
Daclizumab	Zenapax®
Dactinomycin	Cosmegen®
Dalteparin	Fragmin®
Danaparoid	Orgaran®
Dantrolene	Dantrium®
Dapsone	Aczone®
Daptomycin	Cubicin®
Darbepoetin	Aranesp®
Darifenacin	Enablex®
Dasatinib	Sprycel®
Daunorubicin	Cerubidine®
Deferasirox	Exjade®
Deferoxamine (= desferrioxamine)	Desferal®
Delamanid	Deltyba®
Delavirdine	Rescriptor®
Denosumab	Prolia®
Desflurane	Suprane®
Desipramine	Norpramin®
Desirudin	Iprivask®
Desloratadine	Neoclarityn®
Desmopressin	DDAVP®, Desmospray®, Desmotabs®, Nocutil®, Octim®, Stimate®
Desogestrel + ethinylestradiol	Marvelon®
Dexamethasone	Decadron®
Dexetimide	Tremblex®
Dextran	Dextran 40®, RescueFlow®

Table 47.3 Drug names → trade names (cont.)

Drug Name	Trade Name
Diazepam	Diazemuls®, Stesolid®, Tensium®, Valium®
Diazoxide	Eudemine®, Proglycem®
Diclofenac	Arthrotec® (with misoprostol)
	Cataflam®, Difene®, Voltarol®
Dicloxacillin	Dynapen®, Pathocil®
Didanosine	Videx®
Diethylcarbamazine	Ivermectin®
Digoxin	Digitek®, Lanoxin®
Dihydralazine	Nepresol®
Dihydroergotamine	D.E.H.45®, Migranal®
Diltiazem	Dilzem®, Tildiem®
Dimenhydrinate	Dramamine®
Dimercaptopropane sulfonic acid	Dimaval®, Mercuval®
Dimethylaminophenol	4-DMAP®
Dimethylfumarate	Fumaderm®, Tecfidera®
Dimetindene	Fenistil®
Dinoprostone	Cervidil®, Prepidil®, Propess®, Prostin E2®
Diphenhydramine	Benadryl®
Diphenoxylate	Lomotil®
Disopyramide	Norpace®, Rythmodan®
Dobutamine	Dobutrex®
Docetaxel	Taxotere®
Dolutegravir	Tivicay®
Domperidone	Motilium®
Donepezil	Aricept®
Dopamine	Intropin®
Dorzolamide	Trusopt®
Doxacurium	Nuromax®
Doxazosin	Cardura®
Doxepin	Sinequan®
Doxorubicin	Adriamycin®, Adriblastin®, Caelyx®, Myocet®
Doxycycline	Periostat®, Vibramycin®
Doxylamine	Medi-Sleep®, Unisom®
D-Penicillamine	Cuprimine®
Dronabinol	Marinol®
Droperidol	Inapsine®
Drotrecogin	Xigris®
Duloxetine	Cymbalta®, Yentreve®
Dutasteride	Avodart®
E	
Ebastine	Ebastel®
Econazole	Ecostatin®, Gyno-Pevaryl®, Pevaryl®, Spectazole®
Efalizumab	Raptiva®
Efavirenz	Sustiva®
Eletriptan	Relpax®
Empagliflozin	Jardiance®
Enalapril	Innovace®, Vasotec®
Enflurane	Ethrane®
Enfuvirtide	Fuzeon®
Enoxacin	Penetrex®
Enoxaparin	Clexane®, Lovenox®
Entacapone	Comtan®, Comtess®
Entecavir	Baraclude®
Ephedrine	Pretz-D®
Epinephrine (= adrenaline)	Adrenalin®, EpiPen®, Fastject®, Suprarenin®
Epirubicin	Ellence®, Pharmorubicin®
Eplerenone	Inspra®
Epoetin	Eprex®, NeoRecormon®
Eprosartan	Teveten®
Eptifibatide	Integrilin®
Ergometrine (= ergonovine)	Ergotrate®
Ergotamine	Ergomar®, Migril®
Erlotinib	Tarceva®
Erythromycin	Erymax®, Erythrocin®, Erythroped®
Escitalopram	Lexapro®
Esmolol	Brevibloc®
Esomeprazole	Nexium®
Estradiol	Estraderm®, Estrogel®, Evorel®, Vagifem®
Etanercept	Enbrel®
Ethacrynic acid	Edecrin®
Ethambutol	Myambutol®
Ethionamide	Trecator®
Ethopropazine (= profenamine)	Parsidan®, Parsidol®
Ethosuximide	Emeside®, Zarontin®
Etidronate	Didronel®
Etilefrine	Apocretin®
Etofibrate	Lipo-Merz®
Etomidate	Amidate®, Hypnomidate®
Etoposide	Etopophos®, VePesid®
Etretinate	Tegison®
Everolimus	Afinitor®

Table 47.3 Drug names → trade names (cont.)

Drug Name	Trade Name
Exemestane	Aromasin®
Exenatide	Byetta®
Ezetimibe	Ezetrol®, Zetia®
ε-Aminocaproic acid	Amicar®
F	
Famciclovir	Famvir®
Famotidine	Pepcid®
Felbamate	Felbatol®
Felodipine	Plendil®
Felypressin	Octapressin®
Fenofibrate	Antara®, Lipofen®, Tricor®, Triglide®
Fenoterol	Duovent®
Fentanyl	Duragesic®, Sublimaze®
Fexofenadine	Allegra®, Telfast®
Filgrastim	Neupogen®
Finasteride	Propecia®, Proscar®
Flecainide	Tambocor®
Flucloxacillin	Floxapen®
Fluconazole	Diflucan®
Flucytosine	Ancobon®
Fludarabine	Fludara®
Fludrocortisone	Florinef®
Flumazenil	Anexate®, Romazicon®
Flunisolide	Aerobid®, Nasalide®, Syntaris®
Flunitrazepam	Rohypnol®
Fluorouracil	Adrucil®, Efudix®
Fluoxetine	Prozac®
Fluphenazine	Modicate®, Prolixin®
Flurazepam	Dalmane®
Flutamide	Drogenil®, Eulexin®
Fluticasone	Cutivate®, Flixonase®, Flixotide®, Flovent®
Fluvastatin	Lescol®
Fluvoxamine	Faverin®, Luvox®
Fomepizole	Antizol®
Fondaparinux	Arixtra®
Formoterol	Foradil®, Oxis®
Fosaprepitant	Emend®
Foscarnet	Foscavir®
Fosinopril	Monopril®
Fulvestrant	Faslodex®
Furosemide	Lasix®
G	
Gabapentin	Neurontin®
Galantamine	Razadyne®, Reminyl®
Gallopamil	Procorum®
Ganciclovir	Cytovene®
Ganirelix	Orgalutran®
Gelatin colloids	Gelafundin®, Haemaccel®
Gemcitabine	Gemzar®
Gemeprost	Cervagem®
Gemfibrozil	Lopid®
Gentamicin	Cidomycin®, Garamycin®, Genticin®
Glatiramer acetate	Copaxone®
Glibenclamide (= glyburide)	Daonil®, DiaBeta®, Glynase®, Micronase®
Glimepiride	Amaryl®
Gonadorelin	Factrel®
Goserelin	Zoladex®
Granisetron	Kytril®
Griseofulvin	Fulvicin®, Grifulvin®
Guanethidine	Ismelin®
H	
Halofantrine	Halfan®
Haloperidol	Haldol®, Serenace®
Heparin	Calciparine®, Liquemin®
Heparin, low molecular weight	Fragmin®, Fraxiparine®
Hexobarbital	Evipan®
Homatropine	Isopto®
Hydralazine	Apresoline®
Hydrochlorothiazide	Esidrix®
Hydrocortisone (cortisol)	Cortef®, Solu-cortef®
Hydromorphone	Dilaudid®
Hydroxocobalamin	Cyanokit®
Hydroxychloroquine	Plaquenil®
Hydroxyethyl starch	Hespan®
Hydroxyprogesterone acetate	Proluton®
Hydroxyurea	Hydrea®
Hyoscinebutylbromide	Buscopan®
I	
Ibuprofen	Advil®, Brufen®, Motrin®, Nuprin®
Idoxuridine	Dendrid®, Herplex®
Ifosfamide	Ifex®, Mitoxana®
Iloprost	Ventavis®
Imatinib	Gleevec®
Imipenem + cilastatin	Primaxin®

Table 47.3 Drug names → trade names (cont.)

Drug Name	Trade Name
Imipramine	Tofranil®
Indapamide	Lozol®, Natrilix®
Indinavir	Crixivan®
Indomethacin	Indocid®, Indocin®
Infliximab	Remicade®
Insulin aspart	Novolog®
Insulin degludec	Tresiba®
Insulin detemir	Levemir®
Insulin glargine	Lantus®
Insulin glulisine	Apidra®
Insulin human	Actrapid®, Humulin®, Novolin®
Insulin lispro	Humalog®
Interferon gamma	Actimmune®
Interferons	Avonex®, Betaferon®, Imukin®, Inferax®, Intron®, Pegintron®, Roferon®
Ipratropium	Atrovent®
Irbesartan	Aprovel®, Avapro®
Irinotecan	Campto®, Camptosar®
Isoconazole	Gyno-Travogen®, Travogen®
Isoflurane	Forane®
Isoniazid	INH®, Nydrazid®
Isoprenaline (= isoproterenol)	Isuprel®
Isosorbide dinitrate	Isordil®, Sorbitrate®
Isosorbide mononitrate	Imdur®, Ismo®, Monoket®
Isotretinoin	Roaccutane®
Isradipine	Prescal®
Itraconazole	Sporanox®
Ivabradine	Procoralan®
Ivermectin	Stromectol®
K	
Kanamycin	Kantrex®
Ketamine	Ketalar®
Ketoconazole	Nizoral®
Ketorolac	Toradol®
L	
Labetalol	Normodyne®, Trandate®
Lactitol	Importal®
Lactulose	Duphalac®
Lamivudine	Epivir®
Lamotrigine	Lamictal®
Lanreotide	Somatoline®
Lansoprazole	Prevacid®, Zoton®
Latanoprost	Xalatan®
Leflunomide	Arava®
Lenalidomide	Revlimid®
Lenograstim	G-CSF®, Granocyte®
Lepirudin	Refludan®
Letrozole	Femara®
Leuprorelin	Eligard®, Lupron®
Levetiracetam	Keppra®
Levocetirizine	Xysal®
Levodopa	Dopar®, Larodopa®
Levodopa + benserazide	Madopar®
Levodopa + carbidopa	Sinemet®
Levonorgestrel	Microlut®, Mirena®
Levosimendan	Simdax®
Levothyroxine	Eltroxin®, Levoxyl®, Synthroid®
Lidocaine	Xylocaine®, Xylocard®
Lincomycin	Lincocin®
Lindane	Kwell®, Quellada®
Linezolid	Zyvox®
Liothyronine (= triiodothyronine)	Cytomel®
Lisinopril	Carace®, Prinivil®, Zestril®
Lisuride	Dopergin®
Lithium carbonate	Camcolit®, Eskalith®, Priadel®
Lomustine	CCNU®, CeeNu®
Loperamide	Imodium®, Kaopectate II®
Lopinavir	Kaletra®
Loratadine	Alavert®, Claritin®
Lorazepam	Ativan®
Lormetazepam	Noctamid®
Losartan	Cozaar®
Lovastatin	Altoprev®, Mevacor®
Lynestrenol	Ovoresta® (comb.)
Lypressin	Diapid®
M	
Macrogol	Movicol®
Magaldrate	Riopan®
Mannitol	Osmitrol®, Osmofundin®
Maprotiline	Ludiomil®
Maraviroc	Celsentri®
Mebendazole	Vermox®
Mechlorethamine	Mustargen®

Table 47.3 Drug names → trade names (cont.)

Drug Name	Trade Name
Meclizine	Antivert®, Bonine®
Medroxyprogesterone acetate	Depo-Provera®, Provera®
Mefloquine	Lariam®
Megestrol	Megace®
Melatonin	Circadin®
Meloxicam	Mobic®
Melperone	Buronil®, Eunerpan®
Melphalan	Alkeran®
Memantine	Ebixa®, Namenda®
Menadione (Vit. K)	Synkayvit®
Menotropin	Humegon®, Menopur®
Meperidine (= pethidine)	Demerol®
Mepivacaine	Carbocaine®, Polocaine®
Mercaptopurine	Purinethol®
Mesalamine (= mesalazine)	Asacol®, Pentasa®, Rowasa®
Mesna	Mesnex®
Mesterolone	Proviron®
Mestranol (in combination)	Necon®, Ortho-Novum®
Metaproterenol (orciprenaline)	Alupent®
Metenolone	Primobolan®
Metformin	Glucophage®
Methadone	Dolophine®, Physeptone®
Methimazole	Favistan®, Methizol®, Tapazole®
Methohexital	Brevital®
Methotrexate	Folex®, Rheumatrex®
Methotrimeprazine	Nozinan®
Methoxyflurane	Penthrane®
Methylcellulose	Celevac®, Citrucel®
Methyldopa	Aldomet®
Methylergometrine (methylergonovine)	Methergine®
Methylphenidate	Ritalin®
Methyltestosterone	Android®, Oreton®, Testred®
Methysergide	Sansert®
Metipranolol	Optipranolol®
Metoclopramide	Maxolon®, Reglan®
Metoprolol	Betaloc®, Lopressor®
Metronidazole	Flagyl®
Mexiletine	Mexitil®
Mezlocillin	Baypen®
Mianserin	Tolvon®
Miconazole	Daktarin®, Micatin®, Monistat®
Midazolam	Hypnovel®
Mifepristone	Mifeprex®, RU 486®
Miglitol	Glyset®
Milrinone	Primacor®
Minocycline	Minocin®
Minoxidil	Loniten®, Regaine®, Rogaine®
Mirabegron	Betmiga®
Mirtazapine	Remeron®, Zispin®
Misoprostol	Cytotec®
Misoprostol (in combination)	Arthrotec®
Mitomycin	Mutamycin®
Mivacurium	Mivacron®
Mizolastine	Mizollen®
Moclobemide	Manerix®
Modafinil	Provigil®
Molgramostim	Leucomax®
Molsidomin	Corvaton®
Mometasone	Ecural®
Montelukast	Singulair®
Morphine	Duramorph®, MSIR®, MST Continus®, Oramorph®, Roxanol®, Sevredol®
Moxonidine	Physiotens®
Muromonab-CD3	Orthoclone OKT3®
Mycophenolate mofetil	CellCept®
N	
Nabilone	Cesamet®
Nadroparin	Fraxiparine®
Naftifine	Naftin®
Nalbuphine	Nubain®
Nalidixic acid	Negram®
Naloxone	Narcan®
Naltrexone	Revia®
Nandrolone	Deca-Durabolin®
Naphazoline	Privine®
Naphazoline + pheniramine	Naphcon-A®, Visine-A®
Naproxen	Aleve®, Naprosyn®, Synflex®
Naratriptan	Amerge®
Natalizumab	Tysabri®
Nateglinide	Starlix®
Nebivolol	Bystolic®, Nebilet®

Table 47.3 Drug names → trade names (cont.)

Drug Name	Trade Name
Nedocromil	Tilade®
Nefazodone	Serzone®
Nelfinavir	Viracept®
Neomycin	Neofradin®
Neostigmine	Prostigmin®
Netilmicine	Netillin®
Nevirapine	Viramune®
Nicardipine	Cardene®
Nifedipine	Adalat®, Procardia®
Nilotinib	Tasigna®
Nilvadipine	Escor®
Nimodipine	Nimotop®
Nisoldipine	Sular®
Nitrazepam	Mogadon®
Nitrendipine	Baypress®
Nitroglycerin	Nitro-Bid®, Nitro-Dur®, Nitrogard®, Nitrolingual spray®, Transderm-Nitro®
Nitroprusside sodium	Nipride®, Nitropress®
Nitrostigmine	Parathion®
Norepinephrine (= noradrenaline)	Levophed®
Norethisterone	Noriday®, Primolut N®
Norfloxacin	Noroxin®
Nortriptyline	Pamelor®
Noscapine (= narcotine)	Capval®
Nystatin	Mycostatin®, Nilstat®
O	
Obidoxime	Toxogonin®
Octreotide	Sandostatin®
Ofloxacin	Floxin®, Tarivid®
Olanzapine	Zyprexa®
Olodaterol	Striverdi®
Omalizumab	Xolair®
Omeprazole	Losec®, Prilosec®
Ondansetron	Zofran®
Opipramole	Insidon®
Orlistat	Alli®, Xenical®
Oseltamivir	Tamiflu®
Oxacillin	Bactocill®, Prostaphlin®
Oxaliplatin	Eloxatin®
Oxazepam	Serax®
Oxcarbazepine	Trileptal®
Oxiconazole	Oxistat®
Oxprenolol	Trasicor®
Oxycodone	Oxycontin®
Oxymetazoline	Afrin®
Oxytocin	Pitocin®, Syntocinon®
P	
Paclitaxel	Taxol®
Palifermin	Kepivance®
Pamidronate	Aredia®
Pancuronium	Pavulon®
Pantoprazole	Protium®, Protonix®
Parecoxib	Dynastat®
Paromomycin	Humatin®
Paroxetine	Paxil®, Seroxat®
Peginterferon	Pegasys®, Pegintron®
Pegvisomant	Somavert®
Pemetrexed	Alimta®
Penbutalol	Levatol®
Penciclovir	Denavir®
Penicillin G	Bicillin®, Crystapen®
Penicillin V	Calvepen®, Pen-Vee-K®, V-Cillin-K®
Pentamidine	Nebupent®, Pentam 300®
Pentazocine	Fortral®, Talwin®
Pentobarbital	Nembutal®
Pentoxifylline	Trental®
Pergolide	Permax®
Perindopril	Aceon®, Coversyl®
Permethrin	Elimite®, Lyclear®
Perphenazine	Fentazin®, Trilafon®
Phenobarbital	Luminal®
Phenoxybenzamine	Dibenzyline®
Phenprocoumon	Falithrom®, Marcoumar®
Phenylbutazone	Butazolidine®
Phenytoin	Dilantin®
	Epanutin®
Physostigmine	Eserine®, Isopto Eserine®
Phytomenadione	Konakion®
Pilocarpine	Isopto-Carpine®, Salagen®
Pindolol	Visken®
Pioglitazone	Actos®
Pipecuronium	Arduan®
Piperacillin	Pipracil®
Piperacillin + tazobactam	Tazobac®, Zosyn®
Pirenzepine	Gastrozepin®
Piretanide	Eurelix®
Pizotifen	Sanomigran®
Polidocanol	Asclera®

Table 47.3 Drug names → trade names (cont.)

Drug Name	Trade Name
Polymyxin B	Poly-RX®
Posaconazole	Noxafil®
Pralidoxime	Protopam®
Pramipexole	Mirapex®
Pravastatin	Lipostat®, Pravachol®
Prazepam	Centrax®
Praziquantel	Biltricide®
Prazosin	Hypovase®, Minipress®
Prednisolone	Delta-Cortril®, Orapred®, Predfoam®, Prednesol®, Prelone®
Prednisone	Deltasone®
Pregabalin	Lyrica®
Prilocaine	Citanest®, Xylonest®
Primidone	Mysoline®
Probenecid	Probecid®
Procainamide	Procan SR®, Pronestyl®
Procaine	Novocaine®
Procarbazine	Matulane®
Procyclidine	Kemadrin®
Progabide	Gabrene®
Progesterone	Cyclogest®, Gestone®
Proguanil	Paludrine®
Promethazine	Phenergan®
Propafenone	Rythmol®
Propofol	Diprivan®
Propranolol	Inderal®
Pyrantel pamoate	Pin-X®
Pyridostigmine	Mestinon®
Pyrimethamine	Daraprim®
Pyrvinium	Vanquin®
Q	
Quazepam	Doral®
Quetiapine	Seroquel®
Quinacrine	Atabrine®
Quinagolide	Norprolac®
Quinapril	Accupril®, Accupro®
Quinidine	Cardioqin®, Kinidin®, Quinaglute®
Quinine	Qualquin®
R	
Rabeprazole	Aciphex®, Pariet®
Racecadotril	Tiorfan®
Raloxifene	Evista®
Raltegravir	Isentress®
Ramipril	Altace®
Ranibizumab	Lucentis®
Ranitidine	Zantac®
Rasagiline	Azilect®
Rasburicase	Elitek®
Reboxetine	Edronax®
Repaglinide	NovoNorm®, Prandin®
Reserpine	Serpasil®
Reteplase	Retavase®
Reviparin	Clivarin®
Ribavirin	Virazole®
Rifabutin	Mycobutin®
Rifampicin	Rifadin®, Rimactane®
Riociguat	Adempas®
Risedronate	Actonel®
Risperidone	Risperdal®
Ritonavir	Norvir®
Rivastigmine	Exelon®
Rizatriptan	Maxalt®
Rocuronium	Zemuron®
Ropinirole	Requip®
Ropivacaine	Naropin®
Rosiglitazone	Avandia®
Rotigotine	Neupro®
Roxithromycin	Rulide®
Rufinamide	Banzel®
S	
Salazosulfapyridine (sulfasalazine)	Azulfidine®, Salazopyrin®
Salicylic acid	Compound W®, Duofilm®, Keralyt®, Mediplast®, Sebucare®
Salmeterol	Serevent®
Saquinavir	Fortovase®, Invirase®
Scopolamine	Scop®
Selegiline	Eldepryl®, Emsam®
Senna	Senokot®
Sertraline	Lustral®, Zoloft®
Sevoflurane	Ultane®
Sibutramine	Meridia®, Reductil®
Sildenafil	Viagra®
Simethicone	Infacol®, Mylicon®
Simvastatin	Zocor®
Sirolimus	Rapamune®
Sitagliptin	Januvia®
Sitaxentan	Thelin®
Sodium picosulfate	Dulco-lax®, Laxoberal®

Table 47.3 Drug names → trade names (cont.)

Drug Name	Trade Name
Solifenacin	Vesicare®
Somatorelin	GHRH-Ferring®
Somatotropin	Humatrope®
Sorafenib	Nexavar®
Sotalol	Betapace®, Sotacor®
Spironolactone	Aldactone®
Stavudine	Zerit®
Stibogluconate sodium	Pentostam®
Stiripentol	Diacomit®
Streptokinase	Streptase®
Strontium ranelate	Protelos®
Succinylcholine	Anectine®, Quelicin®
Sucralfate	Carafate®
Sufentanil	Sufenta®
Sulfadoxine + pyrimethamine	Fansidar®
Sulfisoxazole	Gantrisin®
Sulpiride	Dolmatil®
Sulprostone	Nalador®
Sumatriptan	Imigran®, Imitrex®
Sunitinib	Sutent®
T	
Tacrine	Cognex®
Tacrolimus	Prograf®, Protopic®
Tadalafil	Cialis®
Talinolol	Cordanum®
Tamoxifen	Nolvadex®
Tamsulosin	Flomax®
Teicoplanin	Targocid®
Telbivudine	Tyzeka®
Telithromycin	Ketek®
Telmisartan	Micardis®
Temazepam	Normison®, Restoril®
Temozolomide	Temodal®
Temsirolimus	Torisel®
Tenecteplase	TNKase®
Teniposide	Vumon®
Terazosin	Hytrin®
Terbutaline	Brethine®, Bricanyl®
Teriparatide	Forsteo®
Tertatolol	Artex®, Prenalex®
Testosterone	Andro LA 200®, Delatestryl®, Depandro100®, Testogel®
Testosterone propionate	Androderm®, Testopel®
Testosterone undecanoate	Aveed®, Nebido®
Tetracaine	Pontocaine®
Tetracycline	Achromycin®, Tetracyn®
Tetrazepam	Musaril®
Tetryzoline (= tetrahydrozoline)	Murine tears plus®, Tyzine®, Visine®
Thalidomide	Thalomid®
Theophylline	Elixophyllin®, Nuelin®, Slo-Phyllin®, Theo-dur®
Thiabendazole	Mintezol®
Thiamine	Vitamin B1®
Thiopental	Pentothal®
Thioridazine	Melleril®
Thrombin	Thrombinar®, Thrombostat®
Thyrotropin	Thyrogen®
Thyroxine	Eltroxin®
Tiagabine	Gabitril®
Ticarcillin	Ticar®
Ticlopidine	Ticlid®
Tigecycline	Tygacil®
Timolol	Blocadren®, Timoptic®, Timoptol®
Tinidazole	Tindamax®
Tinzaparin	Innohep®
Tioconazole	Vagistat-1®
Tiotropium	Spiriva®
Tirofiban	Aggrastat®
Tobramycin	Nebcin®, Tobrex®
Tocainide	Tonocard®
Tolcapone	Tasmar®
Tolterodine	Detrol®, Detrusitol®
Topiramate	Topamax®
Topotecan	Hycamtin®
t-PA (= alteplase)	Activase®
Trabectedin	Yondelis®
Tramadol	Ultram®
Trandolapril	Mavik®
Tranexamic acid	Cyklokapron®
Tranylcypromine	Parnate®
Trastuzumab	Herceptin®
Travoprost	Travatan®
Trazodone	Desyrel®
Triamcinolone	Aristocort®, Kenacort®, Kenalog®, Nasacort®
Triamterene	Dyrenium®
Triamterene + hydrochlorothiazide	Dyazide®

Table 47.3 Drug names → trade names (cont.)

Drug Name	Trade Name
Triazolam	Halcion®
Trichlormethiazide	Metahydrin®, Naqua®
Trifluridine	Viroptic®
Trihexyphenidyl	Artane®
Trimethaphan	Arfonad®
Trimethoprim	Ipral®, Monotrim®, Proloprim®, Trimpex®
Trimethoprim + sulfamethoxazole	Bactrim®, Septra®
Triptorelin	Decapeptyl®, Trelstar Depot®
Tropicamide	Mydral®
Tropisetron	Navoban®
Trospium	Sanctura®
Tubocurarine	Jexin®, Tubarine®
Turoctocog alfa	NovoEight®
Tyrothricin	Tyrozets®
U	
Umoclinidium	Incruse Ellipta®
Urokinase	Abbokinase®, Kinlytic®
V	
Valaciclovir	Valtrex®
Valganciclovir	Valcyte®
Valproic acid	Depakene®, Epilim®
Valsartan	Diovan®
Vancomycin	Vancocin®
Vardenafil	Levitra®
Varenicline	Champix®, Chantix®
Vasopressin	Pitressin®
Vecuronium	Norcuron®
Venlafaxine	Effexor®
Verapamil	Calan®, Isoptin®
Vidarabine	Vira-A®
Vigabatrin	Sabril®
Vilanterol	Ellipta®, Relvar®
Vildagliptin	Galvus®
Vinblastine	Velban®
Vincristine	Oncovin®
Vitamin D	Calciferol®, Drisdol®
Voriconazole	Vfend®
W	
Warfarin	Coumadin®
X	
Xanthinol niacinate	Complamin®
Xipamide	Diurexan®
Xylometazoline	Otrivin®
Z	
Zalcitabine	Hivid®
Zaleplon	Sonata®
Zanamivir	Relenza®
Ziconotide	Prialt®
Zidovudine	Retrovir®
Ziprasidone	Geodon®
Zoledronate	Zometa®
Zolmitriptan	Zomig®
Zolpidem	Ambien®, Stilnoct®
Zopiclone	Zimovane®
Zuclopenthixol	Clopixol®

Table 47.4 Trade names → drug names

Trade name	Drug name
A	
Abbokinase®	Urokinase
Abelcet®	Amphotericin B
Abilify®	Aripiprazole
Accupril®	Quinapril
Accupro®	Quinapril
Aceon®	Perindopril
Achromycin®	Tetracycline
Aciphex®	Rabeprazole
Acthar®	Corticotropin
Actilyse®	Alteplase
Actimmune®	Interferon gamma
Activase®	Alteplase
Activase®	t-PA (= alteplase)
Actonel®	Risedronate
Actos®	Pioglitazone
Actrapid®	Insulin human
Aczone®	Dapsone
Adalat®	Nifedipine
Adempas®	Riociguat
Adrenalin®	Epinephrine (= adrenaline)
Adriamycin®	Doxorubicin
Adriblastin®	Doxorubicin
Adrucil®	Fluorouracil
Advil®	Ibuprofen
Aerobec®	Beclomethasone
Aerobid®	Flunisolide
Afinitor®	Everolimus
Afrin®	Oxymetazoline
Agenerase®	Amprenavir
Aggrastat®	Tirofiban
Akineton®	Biperiden
Aktracin®	Bacitracin + neomycin
Alavert®	Loratadine
Albego®	Camazepam
Aldactone®	Spironolactone
Aldocorten®	Aldosterone
Aldomet®	Methyldopa
Aldrox®	Aluminum hydroxide
Aleve®	Naproxen
Alfenta®	Alfentanil
Alimta®	Pemetrexed
Alkeran®	Melphalan
Allegra®	Fexofenadine
Alli®	Orlistat
Alloferin®	Alcuronium
Alphagan®	Brimonidine
Altace®	Ramipril
Alternagel®	Aluminum hydroxide
Altoprev®	Lovastatin
Alupent®	Metaproterenol (orciprenaline)
Amaryl®	Glimepiride
Ambien®	Zolpidem
Ambisone®	Amphotericin B
Amerge®	Naratriptan
Americaine®	Benzocaine
Amicar®	ε-Aminocaproic acid
Amidate®	Etomidate
Amikin®	Amikacin
Amoxil®	Amoxicillin
Amphocin®	Amphotericin B
Amphotec®	Amphotericin B
Anadin®	Acetaminophen (= paracetamol)
Anbesol®	Benzocaine
Ancobon®	Flucytosine
Andro LA 200®	Testosterone
Androcur®	Cyproterone acetate
Androderm®	Testosterone propionate
Android®	Methyltestosterone
Anectine®	Succinylcholine
Anexate®	Flumazenil
Angettes®	Acetylsalicylic acid
Angiomax®	Bivalirudin
Angiox®	Bivalirudin
Antara®	Fenofibrate
Antivert®	Meclizine
Antizol®	Fomepizole
Apidra®	Insulin glulisine
Apllobal®	Alprenolol
Apocretin®	Etilefrine
Apo-go®	Apomorphine
Apokyn®	Apomorphine
Apresoline®	Hydralazine
Aprovel®	Irbesartan
Aptine®	Alprenolol
Aranesp®	Darbepoetin
Arava®	Leflunomide
Arduan®	Pipecuronium
Aredia®	Pamidronate
Arfonad®	Trimethaphan
Argata®	Argatroban
Aricept®	Donepezil

Table 47.4 Trade names → drug names (cont.)

Trade name	Drug name
Arimidex®	Anastrozole
Aristocort®	Triamcinolone
Arixtra®	Fondaparinux
Aromasin®	Exemestane
Arsumax®	Artesunate
Artane®	Trihexyphenidyl
Artex®	Tertatolol
Arthrotec®	Misoprostol (in combination)
Arthrotec® (with misoprostol)	Diclofenac
Asacol®	Mesalamine (= mesalazine)
Ascabiol®	Benzyl benzoate
Asclera®	Polidocanol
Aspirin®	Acetylsalicylic acid
Atabrine®	Quinacrine
Atacand®	Candesartan
Ativan®	Lorazepam
Atromid-S®	Clofibrate
Atropen®	Atropine
Atrovent®	Ipratropium
Augmentin®	Amoxicillin + clavulanic acid
Avandia®	Rosiglitazone
Avapro®	Irbesartan
Avastin®	Bevacizumab
Aveed®	Testosterone undecanoate
Avicel®	Cellulose
Avloclor®	Chloroquine
Avodart®	Dutasteride
Avonex®	Interferons
Azactam®	Aztreonam
Azilect®	Rasagiline
Azopt®	Brinzolamide
Azulfidine®	Salazosulfapyridine (sulfasalazine)
B	
Baciguent®	Bacitracin + neomycin
Bactocill®	Oxacillin
Bactrim®	Trimethoprim + sulfamethoxazole
	Cotrimoxazole
Banzel®	Rufinamide
Baraclude®	Entecavir
Baypen®	Mezlocillin
Baypress®	Nitrendipine
Beclazone®	Beclomethasone
Becloforte®	Beclomethasone
Becodisks®	Beclomethasone
Beconase®	Beclomethasone
Becotide®	Beclomethasone
Benadryl®	Diphenhydramine
Betaferon®	Interferons
Betaloc®	Metoprolol
Betapace®	Sotalol
Betmiga®	Mirabegron
Betoptic®	Betaxolol
Bezalip®	Bezafibrate
Biaxin®	Clarithromycin
Bicillin®	Penicillin G
Biltricide®	Praziquantel
Bioallethrin®	Allethrin
Bisolvon®	Bromhexine
Blenoxane®	Bleomycin
Blocadren®	Timolol
Bonefos®	Clodronate
Bonine®	Meclizine
Botox®	Botulinum toxin type A
Brethine®	Terbutaline
Brevibloc®	Esmolol
Brevital®	Methohexital
Bricanyl®	Terbutaline
Brufen®	Ibuprofen
Bufferin®	Acetylsalicylic acid
Bumex®	Bumetanide
Burinex®	Bumetanide
Buronil®	Melperone
Buscopan®	Butylscopolamine
	Hyoscine butylbromide
Busilvex®	Busulfan
Buspar®	Buspirone
Butazolidine®	Phenylbutazone
BuTrans®	Buprenorphine
Byetta®	Exenatide
Bystolic®	Nebivolol
C	
Caelyx®	Doxorubicin
Calan®	Verapamil
Calchichew®	Calcium carbonate
Calciferol®	Vitamin D
Calcimar®	Calcitonin
Calciparine®	Heparin
Caltrate®	Calcium carbonate
Calvepen®	Penicillin V

Table 47.4 Trade names → drug names (cont.)

Trade name	Drug name
Camcolit®	Lithium carbonate
Campral®	Acamprosate
Campto®	Irinotecan
Camptosar®	Irinotecan
Cancidas®	Caspofungin
Canesten®	Clotrimazole
Capastat®	Capreomycin
Capoten®	Captopril
Caprin®	Acetylsalicylic acid
Capval®	Noscapine (= narcotine)
Carace®	Lisinopril
Carafate®	Sucralfate
Carbocaine®	Mepivacaine
Cardene®	Nicardipine
Cardicor®	Bisoprolol
Cardioqin®	Quinidine
Cardura®	Doxazosin
Casodex®	Bicalutamide
Cataflam®	Diclofenac
Catapres®	Clonidine
Caverject®	Alprostadil
CCNU®	Lomustine
CeeNu®	Lomustine
Celebrex®	Celecoxib = colecoxib
Celevac®	Methylcellulose
Celexa®	Citalopram
CellCept®	Mycophenolate mofetil
Celsentri®	Maraviroc
Centrax®	Prazepam
Ceporex®	Cefalexin
Cerubidine®	Daunorubicin
Cervagem®	Gemeprost
Cervidil®	Dinoprostone
Cesamet®	Nabilone
Cetrotide®	Cetrorelix
Champix®	Varenicline
Chantix®	Varenicline
Chloromycetin®	Chloramphenicol
Cholestagel®	Colesevelam
Choragon®	Chorionic gonadotropin (HCG)
Cialis®	Tadalafil
Cidomycin®	Gentamicin
Ciloxan®	Ciprofloxacin
Cipramil®	Citalopram
Cipro®	Ciprofloxacin
Ciproxin®	Ciprofloxacin
Circadin®	Melatonin
Citanest®	Prilocaine
Citrucel®	Methylcellulose
Claforan®	Cefotaxime
Claritin®	Loratadine
Cleocin®	Clindamycin
Clexane®	Enoxaparin
Clivarin®	Reviparin
Clomid®	Clomiphene
Clopixol®	Zuclopenthixol
Clozaril®	Clozapine
Codinex®	Codeine (in combinations)
Cogentin®	Benztropine/benzatropine
Cognex®	Tacrine
Colcrys®	Colchicine
Colestid®	Colestipol
Colomycin®	Colistin
Complamin®	Xanthinol niacinate
Compound W®	Salicylic acid
Comtan®	Entacapone
Comtess®	Entacapone
Copaxone®	Glatiramer acetate
Cordanum®	Talinolol
Cordarone®	Amiodarone
Coreg®	Carvedilol
Cortef®	Hydrocortisone (cortisol)
Cortone®	Cortisone
Corvaton®	Molsidomin
Cosmegen®	Dactinomycin
Coumadin®	Warfarin
Coversyl®	Perindopril
Cozaar®	Losartan
Crixivan®	Indinavir
Crystapen®	Penicillin G
Cubicin®	Daptomycin
Cuprimine®	D-Penicillamine
Cutivate®	Fluticasone
Cyanokit®	Hydroxocobalamin
Cyclogest®	Progesterone
Cyklokapron®	Tranexamic acid
Cymbalta®	Duloxetine
Cyprostat®	Cyproterone acetate
Cytamen®	Cyanocobalamin (Vit. B_{12})
Cytomel®	Liothyronine (= triiodothyronine)
Cytosar-U®	Cytarabine
Cytotec®	Misoprostol

Table 47.4 Trade names → drug names (cont.)

Trade name	Drug name
Cytovene®	Ganciclovir
D	
4-DMAP®	Dimethylaminophenol
D.E.H.45®	Dihydroergotamine
Daktarin®	Miconazole
Dalacin®	Clindamycin
Dalmane®	Flurazepam
Dantrium®	Dantrolene
Daonil®	Glibenclamide (= glyburide)
Daraprim®	Pyrimethamine
DDAVP®	Desmopressin
Decadron®	Dexamethasone
Deca-Durabolin®	Nandrolone
Decapeptyl®	Triptorelin
Dedrogyl®	Calcifediol (= vitamin D)
Delatestryl®	Testosterone
Delta-Cortril®	Prednisolone
Deltasone®	Prednisone
Deltyba®	Delamanid
Demerol®	Meperidine (= pethidine)
Denavir®	Penciclovir
Dendrid®	Idoxuridine
Denzapine®	Clozapine
Depakene®	Valproic acid
Depandro100®	Testosterone
Depocyte®	Cytarabine
Depo-Provera®	Medroxyprogesterone acetate
Dermagran®	Aluminum hydroxide
Desferal®	Deferoxamine (= desferrioxamine)
Desmospray®	Desmopressin
Desmotabs®	Desmopressin
Desyrel®	Trazodone
Detrol®	Tolterodine
Detrusitol®	Tolterodine
Dextran40®	Dextran
DiaBeta®	Glibenclamide (= glyburide)
Diacomit®	Stiripentol
Diamox®	Acetazolamide
Diapid®	Lypressin
Diazemuls®	Diazepam
Dibenzyline®	Phenoxybenzamine
Didronel®	Etidronate
Difene®	Diclofenac
Diflucan®	Fluconazole
Digitek®	Digoxin
Dilantin®	Phenytoin
Dilaudid®	Hydromorphone
Dilzem®	Diltiazem
Dimaval®	Dimercaptopropane sulfonic acid
Diovan®	Valsartan
Diprivan®	Propofol
Disprin®	Aspirin
Distaclor®	Cefaclor
Diurexan®	Xipamide
Dixarit®	Clonidine
Dobutrex®	Dobutamine
Dolmatil®	Sulpiride
Dolophine®	Methadone
Dopar®	Levodopa
Dopergin®	Lisuride
Doral®	Quazepam
Dostinex®	Cabergoline
Dramamine®	Dimenhydrinate
Drisdol®	Vitamin D
Drogenil®	Flutamide
Dtic-Dome®	Dacarbazine
Dulcolax®	Bisacodyl
Dulco-lax®	Sodium picosulfate
Duofilm®	Salicylic acid
Duovent®	Fenoterol
Duphalac®	Lactulose
Duragesic®	Fentanyl
Duramorph®	Morphine
Dyazide®	Triamterene + hydrochlorothiazide
Dynapen®	Dicloxacillin
Dynastat®	Parecoxib
Dyrenium®	Triamterene
Dyspamet®	Cimetidine
Dysport®	Botulinum toxin type A
E	
Ebastel®	Ebastine
Ebixa®	Memantine
Ecalta®	Anidulafungin
Ecostatin®	Econazole
Ecotrin®	Acetylsalicylic acid
Ecural®	Mometasone
Edecrin®	Ethacrynic acid
Edex®	Alprostadil
Edronax®	Reboxetine
Effexor®	Venlafaxine
Efudix®	Fluorouracil
Elavil®	Amitriptyline

Table 47.4 Trade names → drug names (cont.)

Trade name	Drug name
Eldepryl®	Selegiline
Eligard®	Leuprorelin
Elimite®	Permethrin
Elitek®	Rasburicase
Elixophyllin®	Theophylline
Ellence®	Epirubicin
Ellipta®	Vilanterol
Eloxatin®	Oxaliplatin
Elspar®	Asparaginase (= crisantaspase)
Eltroxin®	Levothyroxine
	Thyroxine
Embolex®	Certoparin
Emcor®	Bisoprolol
Emend®	Aprepitant
	Fosaprepitant
Emeside®	Ethosuximide
Eminase®	Anistreplase
Emsam®	Selegiline
Enablex®	Darifenacin
Enbrel®	Etanercept
Endep®	Amitriptyline
Endoxana®	Cyclophosphamide
Entocort EC®	Budesonide
Epanutin®	Phenytoin
Epilim®	Valproic acid
EpiPen®	Epinephrine (= adrenaline)
Epivir®	Lamivudine
Eprex®	Epoetin
Eraxis®	Anidulafungin
Erbitux®	Cetuximab
Ergomar®	Ergotamine
Ergotrate®	Ergometrine (= ergonovine)
Erymax®	Erythromycin
Erythrocin®	Erythromycin
Erythroped®	Erythromycin
Escor®	Nilvadipine
Eserine®	Physostigmine
Esidrix®	Hydrochlorothiazide
Eskalith®	Lithium carbonate
Estraderm®	Estradiol
Estrogel®	Estradiol
Ethrane®	Enflurane
Etopophos®	Etoposide
Eudemine®	Diazoxide
Eulexin®	Flutamide
Eunerpan®	Melperone
Eurelix®	Piretanide
Evipan®	Hexobarbital
Evista®	Raloxifene
Evorel®	Estradiol
Exelon®	Rivastigmine
Exjade®	Deferasirox
Ezetrol®	Ezetimibe
F	
Factrel®	Gonadorelin
Falcigo®	Artesunate
Falithrom®	Phenprocoumon
Famvir®	Famciclovir
Fansidar®	Sulfadoxine + pyrimethamine
Faslodex®	Fulvestrant
Fastject®	Epinephrine (= adrenaline)
Faverin®	Fluvoxamine
Favistan®	Methimazole
Felbatol®	Felbamate
Femara®	Letrozole
Fenistil®	Dimetindene
Fentazin®	Perphenazine
Fiboran®	Aprindine
Flagyl®	Metronidazole
Flixonase®	Fluticasone
Flixotide®	Fluticasone
Flomax®	Tamsulosin
Florinef®	Fludrocortisone
Flovent®	Fluticasone
Floxapen®	Flucloxacillin
Floxin®	Ofloxacin
Fludara®	Fludarabine
Fluimucil®	Acetylcysteine
Folex®	Methotrexate
Foradil®	Formoterol
Forane®	Isoflurane
Forsteo®	Teriparatide
Fortovase®	Saquinavir
Fortral®	Pentazocine
Fortum®	Ceftazidime
Fosamax®	Alendronate
Foscavir®	Foscarnet
Fragmin®	Dalteparin
	Heparin, low molecular weight
Fraxiparine®	Heparin, low molecular weight
	Nadroparin
Fulvicin®	Griseofulvin

Table 47.4 Trade names → drug names (cont.)

Trade name	Drug name
Fumaderm®	Dimethylfumarate
Fungilin®	Amphotericin B
Fungizone®	Amphotericin B
Fuzeon®	Enfuvirtide
G	
Gabitril®	Tiagabine
Gabrene®	Progabide
Galvus®	Vildagliptin
Ganfort®	Bimatoprost
Gantrisin®	Sulfisoxazole
Garamycin®	Gentamicin
Gastrozepin®	Pirenzepine
G-CSF®	Lenograstim
Gelafundin®	Gelatin colloids
Gemzar®	Gemcitabine
Genacote®	Acetylsalicylic acid
Genapap®	Acetaminophen (= paracetamol)
Genticin®	Gentamicin
Geocillin®	Carbenicillin
Geodon®	Ziprasidone
Gestafortin®	Chlormadinone
Gestone®	Progesterone
GHRH-Ferring®	Somatorelin
Glauconex®	Befunolol
Gleevec®	Imatinib
Glucobay®	Acarbose
Glucophage®	Metformin
Glynase®	Glibenclamide (= glyburide)
Glyset®	Miglitol
Granocyte®	Lenograstim
Grifulvin®	Griseofulvin
Gubernal®	Alprenolol
Gyne-Lotrimin®	Clotrimazole
Gyno-Pevaryl®	Econazole
Gyno-Travogen®	Isoconazole
H	
Haemaccel®	Gelatin colloids
Halcion®	Triazolam
Haldol®	Haloperidol
Halfan®	Halofantrine
Heminevrin®	Clomethiazole
Hepsera®	Adefovir
Herceptin®	Trastuzumab
Herplex®	Idoxuridine
Hespan®	Hydroxyethyl starch
Hismanal®	Astemizole
Hivid®	Zalcitabine
Humalog®	Insulin lispro
Humatin®	Paromomycin
Humatrope®	Somatotropin
Humegon®	Menotropin
Humira®	Adalimumab
Humulin®	Insulin human
Hycamtin®	Topotecan
Hydrea®	Hydroxyurea
Hygroton®	Chlorthalidone
Hypertensin®	Angiotensin amide
Hypnomidate®	Etomidate
Hypnovel®	Midazolam
Hypovase®	Prazosin
Hytrin®	Terazosin
I	
Ifex®	Ifosfamide
Imdur®	Isosorbide mononitrate
Imigran®	Sumatriptan
Imitrex®	Sumatriptan
Imodium®	Loperamide
Importal®	Lactitol
Imukin®	Interferons
Imuran®	Azathioprine
Inapsine®	Droperidol
Incruse Ellipta®	Umoclinidium
Inderal®	Propranolol
Indocid®	Indomethacin
Indocin®	Indomethacin
Infacol®	Simethicone
Inferax®	Interferons
INH®	Isoniazid
Innohep®	Tinzaparin
Innovace®	Enalapril
Inocor®	Amrinone
Insidon®	Opipramole
Inspra®	Eplerenone
Intal®	Cromoglicate (= cromolyn)
Integrilin®	Eptifibatide
Intron®	Interferons
Intropin®	Dopamine
Invirase®	Saquinavir
Invokana®	Canagliflozin
Iopidine®	Apraclonidine
Ipral®	Trimethoprim
Iprivask®	Desirudin

Table 47.4 Trade names → drug names (cont.)

Trade name	Drug name
Iscover®	Clopidogrel
Isentress®	Raltegravir
Ismelin®	Guanethidine
Ismo®	Isosorbide mononitrate
Isoptin®	Verapamil
Isopto Eserine®	Physostigmine
Isopto®	Homatropine
Isopto-Carpine®	Pilocarpine
Isordil®	Isosorbide dinitrate
Istin®	Amlodipine
Isuprel®	Isoprenaline (= isoproterenol)
Ivermectin®	Diethylcarbamazine
J	
Januvia®	Sitagliptin
Jardiance®	Empagliflozin
Jexin®	Tubocurarine
K	
Kaletra®	Lopinavir
Kantrex®	Kanamycin
Kaopectate II®	Loperamide
Keflex®	Cefalexin
Kemadrin®	Procyclidine
Kemicetine®	Chloramphenicol
Kenacort®	Triamcinolone
Kenalog®	Triamcinolone
Kepivance®	Palifermin
Keppra®	Levetiracetam
Keralyt®	Salicylic acid
Kerlone®	Betaxolol
Ketalar®	Ketamine
Ketek®	Telithromycin
Kineret®	Anakinra
Kinidin®	Quinidine
Kinlytic®	Urokinase
Klacid®	Clarithromycin
Klonopin®	Clonazepam
Konakion®	Phytomenadione
Kwell®	Lindane
Kytril®	Granisetron
L	
Lamictal®	Lamotrigine
Lamprene®	Clofazimine
Lanoxin®	Digoxin
Lantus®	Insulin glargine
Largactil®	Chlorpromazine
Lariam®	Mefloquine
Larodopa®	Levodopa
Lasix®	Furosemide
Laxoberal®	Sodium picosulfate
Lendormin®	Brotizolam
Lescol®	Fluvastatin
Leucomax®	Molgramostim
Leukeran®	Chlorambucil
Leustatin®	Cladribine
Levatol®	Penbutalol
Levemir®	Insulin detemir
Levitra®	Vardenafil
Levophed®	Norepinephrine (= noradrenaline)
Levoxyl®	Levothyroxine
Lexapro®	Escitalopram
Lexotan®	Bromazepam
Librium®	Chlordiazepoxide
Lincocin®	Lincomycin
Lioresal®	Baclofen
Lipitor®	Atorvastatin
Lipofen®	Fenofibrate
Lipo-Merz®	Etofibrate
Lipostat®	Pravastatin
Liquemin®	Heparin
Litak®	Cladribine
Loceryl®	Amorolfine
Lodosyn®	Carbidopa
Lomotil®	Diphenoxylate
Loniten®	Minoxidil
Lopid®	Gemfibrozil
Lopressor®	Metoprolol
Losec®	Omeprazole
Lotensin®	Benazepril
Lovenox®	Enoxaparin
Lozol®	Indapamide
Lucentis®	Ranibizumab
Ludiomil®	Maprotiline
Lumigan®	Bimatoprost
Luminal®	Phenobarbital
Lupron®	Leuprorelin
Lustral®	Sertraline
Luvox®	Fluvoxamine
Lyclear®	Permethrin
Lyrica®	Pregabalin
Lysovir®	Amantadine
M	
Madopar®	Levodopa + benserazide

Table 47.4 Trade names → drug names (cont.)

Trade name	Drug name
Malarone®	Atovaquone+ proguanil
Manerix®	Moclobemide
Marcoumar®	Phenprocoumon
Marinol®	Dronabinol
Marvelon®	Desogestrel + ethinylestradiol
Matulane®	Procarbazine
Mavik®	Trandolapril
Maxalt®	Rizatriptan
Maxolon®	Metoclopramide
Mediplast®	Salicylic acid
Medi-Sleep®	Doxylamine
Megace®	Megestrol
Melleril®	Thioridazine
Menopur®	Menotropin
Mepron®	Atovaquone
Mercuval®	Dimercaptopropane sulfonic acid
Meridia®	Sibutramine
Mesnex®	Mesna
Mestinon®	Pyridostigmine
Metahydrin®	Trichlormethiazide
Methergine®	Methylergometrine (methyl-ergonovine)
Methizol®	Methimazole
Mevacor®	Lovastatin
Mexitil®	Mexiletine
Miacalcin®	Calcitonin
Micardis®	Telmisartan
Micatin®	Miconazole
Microlut®	Levonorgestrel
Micronase®	Glibenclamide (= glyburide)
Midamor®	Amiloride
Mifeprex®	Mifepristone
Migranal®	Dihydroergotamine
Migril®	Ergotamine
Mimpara®	Cinacalcet
Minipress®	Prazosin
Minocin®	Minocycline
Mintezol®	Thiabendazole
Miostat®	Carbachol
Mirapex®	Pramipexole
Mirena®	Levonorgestrel
Mitoxana®	Ifosfamide
Mivacron®	Mivacurium
Mizollen®	Mizolastine
Mobic®	Meloxicam
Modicate®	Fluphenazine
Moduret®	Amiloride + hydrochlorothiazide
Mogadon®	Nitrazepam
Monistat®	Miconazole
Monoket®	Isosorbide mononitrate
Monopril®	Fosinopril
Monotrim®	Trimethoprim
Motilium®	Domperidone
Motrin®	Ibuprofen
Movicol®	Macrogol
MSIR®	Morphine
MST Continus®	Morphine
Mucomyst®	Acetylcysteine
Murine tears plus®	Tetryzoline (= tetrahydrozoline)
Musaril®	Tetrazepam
Muse®	Alprostadil
Mustargen®	Mechlorethamine
Mutamycin®	Mitomycin
Myambutol®	Ethambutol
Mycelex®	Clotrimazole
Mycobutin®	Rifabutin
Mycostatin®	Nystatin
Mydral®	Tropicamide
Myleran®	Busulfan
Mylicon®	Simethicone
Myobloc®	Botulinum toxin type B
Myocet®	Doxorubicin
Myocrisin®	Aurothiomalate sodium
Mysoline®	Primidone
N	
Naftin®	Naftifine
Nalador®	Sulprostone
Namenda®	Memantine
Naphcon-A®	Naphazoline + pheniramine
Naprosyn®	Naproxen
Naqua®	Trichlormethiazide
Narcan®	Naloxone
Naropin®	Ropivacaine
Nasacort®	Triamcinolone
Nasalcrom®	Cromoglicate (= cromolyn)
Nasalide®	Flunisolide
Nascobal®	Cyanocobalamin (Vit. B_{12})
Natrilix®	Indapamide
Navispare®	Amiloride + hydrochlorothiazide
Navoban®	Tropisetron
Nebcin®	Tobramycin
Nebido®	Testosterone undecanoate

Table 47.4 Trade names → drug names (cont.)

Trade name	Drug name
Nebilet®	Nebivolol
Nebupent®	Pentamidine
Necon®	Mestranol (in combination)
Negram®	Nalidixic acid
Nembutal®	Pentobarbital
Neoclarityn®	Desloratadine
Neo-Cytamen®	Cyanocobalamin (Vit. B_{12})
Neofradin®	Neomycin
Neo-Mercazole®	Carbimazole
Neoral®	Ciclosporin (= cyclosporin A)
NeoRecormon®	Epoetin
Neosporin®	Bacitracin + neomycin + polymyxin B
Neotigason®	Acitretin
Nepresol®	Dihydralazine
Nesacaine®	Chloroprocaine
Netillin®	Netilmicin
Neupogen®	Filgrastim
Neupro®	Rotigotine
NeuroBloc®	Botulinum toxin type B
Neurontin®	Gabapentin
Nexavar®	Sorafenib
Nexium®	Esomeprazole
Nilstat®	Nystatin
Nimotop®	Nimodipine
Nipride®	Nitroprusside sodium
Nitro-Bid®	Nitroglycerin
Nitro-Dur®	Nitroglycerin
Nitrogard®	Nitroglycerin
Nitrolingual spray®	Nitroglycerin
Nitropress®	Nitroprusside sodium
Nivaquine®	Chloroquine
Nizoral®	Ketoconazole
Noctamid®	Lormetazepam
Noctec®	Chloral hydrate
Nocutil®	Desmopressin
Nolvadex®	Tamoxifen
Norcuron®	Vecuronium
Noriday®	Norethisterone
Normiflo®	Ardeparin
Normison®	Temazepam
Normodyne®	Labetalol
Noroxin®	Norfloxacin
Norpace®	Disopyramide
Norpramin®	Desipramine
Norprolac®	Quinagolide
Norvasc®	Amlodipine
Norvir®	Ritonavir
Novocaine®	Procaine
Novodigal®	Acetyldigoxin
NovoEight®	Turoctocog alfa
Novolin®	Insulin human
Novolog®	Insulin aspart
NovoNorm®	Repaglinide
Noxafil®	Posaconazole
Nozinan®	Methotrimeprazine
Nubain®	Nalbuphine
Nuelin®	Theophylline
Nuprin®	Ibuprofen
Nuromax®	Doxacurium
Nu-Seals®	Aspirin
Nydrazid®	Isoniazid
O	
Octapressin®	Felypressin
Octim®	Desmopressin
Oculinum®	Botulinum toxin type A
Ocupress®	Carteolol
Olbetam®	Acipimox
Omnipen®	Ampicillin
Oncovin®	Vincristine
Ondogyne®	Cyclofenil
Opticrom®	Cromoglicate (= cromolyn)
Optipranolol®	Metipranolol
Orajel®	Benzocaine
Oramorph®	Morphine
Orapred®	Prednisolone
Orencia®	Abatacept
Oreton®	Methyltestosterone
Orgaran®	Danaparoid
Orgalutran®	Ganirelix
Orthoclone OKT3®	Muromonab-CD3
Ortho-Novum®	Mestranol (in combination)
Osmitrol®	Mannitol
Osmofundin®	Mannitol
Otrivin®	Xylometazoline
Ovitrelle®	Chorionic gonadotropin (HCG)
Ovoresta® (comb.)	Lynestrenol
Oxis®	Formoterol
Oxistat®	Oxiconazole
Oxycontin®	Oxycodone

Table 47.4 Trade names → drug names (cont.)

Trade name	Drug name
P	
Pabal®	Carbetocin
Paludrine®	Proguanil
Pamba®	Aminomethylbenzoic acid
Pamelor®	Nortriptyline
Panadol®	Acetaminophen (= paracetamol)
Paraplatin®	Carboplatin
Parathion®	Nitrostigmine
Pariet®	Rabeprazole
Parkinsan®	Budipine
Parlodel®	Bromocriptine
Parnate®	Tranylcypromine
Parsidan®	Ethopropazine (= profenamine)
Parsidol®	Ethopropazine (= profenamine)
Parvolex®	Acetylcysteine
Pathocil®	Dicloxacillin
Pavulon®	Pancuronium
Paxil®	Paroxetine
Pegasys®	Peginterferon
Pegintron®	Interferons
	Peginterferon
Penbritin®	Ampicillin
Penetrex®	Enoxacin
Pentam 300®	Pentamidine
Pentasa®	Mesalamine (= mesalazine)
Penthrane®	Methoxyflurane
Pentostam®	Stibogluconate sodium
Pentothal®	Thiopental
Pen-Vee-K®	Penicillin V
Pepcid®	Famotidine
Pepto-Bismol®	Bismuth subsalicylate
Periostat®	Doxycycline
Permax®	Pergolide
Pevaryl®	Econazole
Pharmorubicin®	Epirubicin
Phenergan®	Promethazine
Phyllocontin®	Aminophylline
Physeptone®	Methadone
Physiotens®	Moxonidine
Pin-X®	Pyrantel pamoate
Pipracil®	Piperacillin
Pitocin®	Oxytocin
Pitressin®	Vasopressin
Plaquenil®	Hydroxychloroquine
Plasmotrim®	Artesunate
Platinol®	Cisplatin
Plavix®	Clopidogrel
Plenaxis®	Abarelix
Plendil®	Felodipine
Pletal®	Cilostazol
Polocaine®	Mepivacaine
Poly-RX®	Polymyxin B
Pontocaine®	Tetracaine
Pradaxa®	Dabigatran
Prandin®	Repaglinide
Pravachol®	Pravastatin
Precose®	Acarbose
Predfoam®	Prednisolone
Prednesol®	Prednisolone
Pregnyl®	Chorionic gonadotropin (HCG)
Prelone®	Prednisolone
Prenalex®	Tertatolol
Prepidil®	Dinoprostone
Prescal®	Isradipine
Pretz-D®	Ephedrine
Prevacid®	Lansoprazole
Prevalite®	Cholestyramine
Priadel®	Lithium carbonate
Prialt®	Ziconotide
Prilosec®	Omeprazole
Primacor®	Milrinone
Primaxin®	Imipenem + cilastatin
Primobolan®	Metenolone
Primolut N®	Norethisterone
Principen®	Ampicillin
Prinivil®	Lisinopril
Privine®	Naphazoline
Probecid®	Probenecid
Procan SR®	Procainamide
Procardia®	Nifedipine
Procoralan®	Ivabradine
Procorum®	Gallopamil
Proglycem®	Diazoxide
Prograf®	Tacrolimus
Prolia®	Denosumab
Prolixin®	Fluphenazine
Proloprim®	Trimethoprim
Proluton®	Hydroxyprogesterone acetate
Promixin®	Colistin
Pronestyl®	Procainamide
Propecia®	Finasteride
Propess®	Dinoprostone

Table 47.4 Trade names → drug names (cont.)

Trade name	Drug name
Propulsid®	Cisapride
Proscar®	Finasteride
Prostaphlin®	Oxacillin
Prostigmin®	Neostigmine
Prostin E2®	Dinoprostone
Protelos®	Strontium ranelate
Protium®	Pantoprazole
Protonix®	Pantoprazole
Protopam®	Pralidoxime
Protopic®	Tacrolimus
Proventil®	Albuterol see Salbutamol
Provera®	Medroxyprogesterone acetate
Provigil®	Modafinil
Proviron®	Mesterolone
Prozac®	Fluoxetine
Pulmicort®	Budesonide
Purinethol®	Mercaptopurine
Q	
Qualquin®	Quinine
Quelicin®	Succinylcholine
Quellada®	Lindane
Questran®	Cholestyramine
Quinaglute®	Quinidine
Qvar®	Beclomethasone
R	
Rapamune®	Sirolimus
Rapifen®	Alfentanil
Raptiva®	Efalizumab
Rasilez®	Aliskiren
Razadyne®	Galantamine
Reductil®	Sibutramine
Refludan®	Lepirudin
Regaine®	Minoxidil
Reglan®	Metoclopramide
Relenza®	Zanamivir
Relpax®	Eletriptan
Relvar®	Vilanterol
Remeron®	Mirtazapine
Remicade®	Infliximab
Reminyl®	Galantamine
ReoPro®	Abciximab
Requip®	Ropinirole
Rescriptor®	Delavirdine
RescueFlow®	Dextran
Restoril®	Temazepam
Retavase®	Reteplase
Retrovir®	Zidovudine
Revia®	Naltrexone
Revlimid®	Lenalidomide
Rheumatrex®	Methotrexate
Rheumox®	Azapropazone
Rhinocort®	Budesonide
Riamet®	Artemether + lumefantrine
Ridaura®	Auranofin
Rifadin®	Rifampicin
Rimactane®	Rifampicin
Riopan®	Magaldrate
Risperdal®	Risperidone
Ritalin®	Methylphenidate
Rivotril®	Clonazepam
Roaccutane®	Isotretinoin
Robitussin®	Codeine (in combinations)
Rocaltrol®	Calcitriol
Rocephin®	Ceftriaxone
Roferon®	Interferons
Rogaine®	Minoxidil
Rohypnol®	Flunitrazepam
Romazicon®	Flumazenil
Rowasa®	Mesalamine (= mesalazine)
Roxanol®	Morphine
RU 486®	Mifepristone
Rulide®	Roxithromycin
Rynacrom®	Cromoglicate (= cromolyn)
Rythmodan®	Disopyramide
Rythmol®	Propafenone
S	
Sabril®	Vigabatrin
Salagen®	Pilocarpine
Salazopyrin®	Salazosulfapyridine (sulfasalazine)
Sanctura®	Trospium
Sandimmune®	Ciclosporin (= cyclosporin A)
Sandostatin®	Octreotide
Sanomigran®	Pizotifen
Sansert®	Methysergide
Scop®	Scopolamine
Sebucare®	Salicylic acid
Sectral®	Acebutolol
Securopen®	Azlocillin
Selectol®	Celiprolol
Senokot®	Senna
Septra®	Trimethoprim + sulfamethoxazole

Table 47.4 Trade names → drug names (cont.)

Trade name	Drug name
Septrin®	Cotrimoxazole
Serax®	Oxazepam
Serenace®	Haloperidol
Serevent®	Salmeterol
Seromycin®	Cycloserine
Seroquel®	Quetiapine
Seroxat®	Paroxetine
Serpasil®	Reserpine
Serzone®	Nefazodone
Sevredol®	Morphine
Sexovid®	Cyclofenil
Simdax®	Levosimendan
Simulect®	Basiliximab
Sinemet®	Levodopa + carbidopa
Sinequan®	Doxepin
Singulair®	Montelukast
Sinthrome®	Acenocoumarin (= nicoumalone)
Sirturo®	Bedaquiline
Slo-Phyllin®	Theophylline
Soldactone®	Canrenone
Solganal®	Aurothioglucose
Solu-cortef®	Hydrocortisone (cortisol)
Somatoline®	Lanreotide
Somavert®	Pegvisomant
Sonata®	Zaleplon
Sorbitrate®	Isosorbide dinitrate
Soriatane®	Acitretin
Sotacor®	Sotalol
Soventol®	Bamipine
Spectazole®	Econazole
Spiriva®	Tiotropium
Sporanox®	Itraconazole
Sprycel®	Dasatinib
Starlix®	Nateglinide
Stesolid®	Diazepam
Stilnoct®	Zolpidem
Stimate®	Desmopressin
Strattera®	Atomoxetine
Streptase®	Streptokinase
Stresson®	Bunitrolol
Striverdi®	Olodaterol
Stromectol®	Ivermectin
Suacron®	Carazolol
Sublimaze®	Fentanyl
Subutex®	Buprenorphine
Sufenta®	Sufentanil
Sular®	Nisoldipine
Suprane®	Desflurane
Suprarenin®	Epinephrine (= adrenaline)
Suprecur®	Buserelin
Suprefact®	Buserelin
Sustiva®	Efavirenz
Sutent®	Sunitinib
Symmetrel®	Amantadine
Synacthen®	Corticotropin
Synflex®	Naproxen
Synkayvit®	Menadione (Vit. K)
Syntaris®	Flunisolide
Synthroid®	Levothyroxine
Syntocinon®	Oxytocin
T	
Tagamet®	Cimetidine
Talwin®	Pentazocine
Tambocor®	Flecainide
Tamiflu®	Oseltamivir
Tapazole®	Methimazole
Tarceva®	Erlotinib
Targocid®	Teicoplanin
Tarivid®	Ofloxacin
Tasigna®	Nilotinib
Tasmar®	Tolcapone
Tavegil®	Clemastine
Tavist®	Clemastine
Taxol®	Paclitaxel
Taxotere®	Docetaxel
Tazobac®	Piperacillin + tazobactam
Tecfidera®	Dimethylfumarate
Tegison®	Etretinate
Tegretol®	Carbamazepine
Tekturna®	Aliskiren
Telfast®	Fexofenadine
Temgesic®	Buprenorphine
Temodal®	Temozolomide
Tenormin®	Atenolol
Tensium®	Diazepam
Testogel®	Testosterone
Testopel®	Testosterone propionate
Testred®	Methyltestosterone
Tetracyn®	Tetracycline
Teveten®	Eprosartan
Thalomid®	Thalidomide
Thelin®	Sitaxentan

Table 47.4 Trade names → drug names (cont.)

Trade name	Drug name
Theo-dur®	Theophylline
Thorazine®	Chlorpromazine
Thrombinar®	Thrombin
Thrombostat®	Thrombin
Thyrogen®	Thyrotropin
Ticar®	Ticarcillin
Ticlid®	Ticlopidine
Tilade®	Nedocromil
Tildiem®	Diltiazem
Timoptic®	Timolol
Timoptol®	Timolol
Tindamax®	Tinidazole
Tiorfan®	Racecadotril
Tivicay®	Dolutegravir
TNKase®	Tenecteplase
Tobrex®	Tobramycin
Tofranil®	Imipramine
Tolvon®	Mianserin
Tonocard®	Tocainide
Topamax®	Topiramate
Toradol®	Ketorolac
Torisel®	Temsirolimus
Tornalate®	Bitolterol
Toxogonin®	Obidoxime
Tracleer®	Bosentan
Tracrium®	Atracurium
Tractocile®	Atosiban
Trandate®	Labetalol
Transderm-Nitro®	Nitroglycerin
Tranxene®	Clorazepate
Trasicor®	Oxprenolol
Travatan®	Travoprost
Travogen®	Isoconazole
Trecator®	Ethionamide
Trelstar Depot®	Triptorelin
Tremblex®	Dexetimide
Trental®	Pentoxifylline
Tresiba®	Insulin degludec
Tricor®	Fenofibrate
Triglide®	Fenofibrate
Trilafon®	Perphenazine
Trileptal®	Oxcarbazepine
Trimox®	Amoxicillin
Trimpex®	Trimethoprim
Triptafen®	Amitriptyline + perphenazine
Truoxin®	Ciprofloxacin
Trusopt®	Dorzolamide
Tryptizol®	Amitriptyline
Tubarine®	Tubocurarine
Tygacil®	Tigecycline
Tylenol®	Acetaminophen (= paracetamol)
Tyrozets®	Tyrothricin
Tysabri®	Natalizumab
Tyzeka®	Telbivudine
Tyzine®	Tetryzoline (= tetrahydrozoline)
U	
Ultane®	Sevoflurane
Ultracain®	Articaine
Ultram®	Tramadol
Unasyn®	Ampicillin + sulbactam
Unisom®	Doxylamine
UroXatral®	Alfuzosin
V	
Vagifem®	Estradiol
Vagistat-1®	Tioconazole
Valcyte®	Valganciclovir
Valium®	Diazepam
Valorin®	Acetaminophen (= paracetamol)
Valtrex®	Valaciclovir
Vancocin®	Vancomycin
Vanquin®	Pyrvinium
Vascace®	Cilazapril
Vasotec®	Enalapril
V-Cillin-K®	Penicillin V
Velban®	Vinblastine
Velcade®	Bortezomib
Venactone®	Canrenone
Ventavis®	Iloprost
Ventolin®	Albuterol see Salbutamol
VePesid®	Etoposide
Vermox®	Mebendazole
Vesicare®	Solifenacin
Vfend®	Voriconazole
Viagra®	Sildenafil
Vibramycin®	Doxycycline
Videx®	Didanosine
Vira-A®	Vidarabine
Viracept®	Nelfinavir
Viramune®	Nevirapine
Virazole®	Ribavirin
Viridal®	Alprostadil
Viroptic®	Trifluridine

Table 47.4 Trade names → drug names (cont.)

Trade name	Drug name
Visine®	Tetryzoline (= tetrahydrozoline)
Visine-A®	Naphazoline + pheniramine
Visken®	Pindolol
Vitamin B1®	Thiamine
Vividrin®	Cromoglicate (= cromolyn)
Voltarol®	Diclofenac
Vumon®	Teniposide
W	
Welchol®	Colesevelam
Wellbutrin®	Bupropion
Welldorm®	Chloral hydrate
Wellvone®	Atovaquone
X	
Xalatan®	Latanoprost
Xanax®	Alprazolam
Xatral®	Alfuzosin
Xeloda®	Capecitabine
Xenical®	Orlistat
Xigris®	Drotrecogin
Xolair®	Omalizumab
Xylocaine®	Lidocaine
Xylocard®	Lidocaine
Xylonest®	Prilocaine
Xysal®	Levocetirizine
Y	
Yentreve®	Duloxetine
Yondelis®	Trabectedin
Z	
Zantac®	Ranitidine
Zaponex®	Clozapine
Zarontin®	Ethosuximide
Zebeta®	Bisoprolol
Zemuron®	Rocuronium
Zenapax®	Daclizumab
Zerit®	Stavudine
Zestril®	Lisinopril
Zetia®	Ezetimibe
Ziagen®	Abacavir
Zimovane®	Zopiclone
Zispin®	Mirtazapine
Zithromax®	Azithromycin
Zocor®	Simvastatin
Zofran®	Ondansetron
Zoladex®	Goserelin
Zoloft®	Sertraline
Zometa®	Zoledronate
Zomig®	Zolmitriptan
Zosyn®	Piperacillin + tazobactam
Zoton®	Lansoprazole
Zovirax®	Aciclovir
Zyban®	Bupropion
Zyloprim®	Allopurinol
Zyloric®	Allopurinol
Zyprexa®	Olanzapine
Zirtek®	Cetirizine
Zyvox®	Linezolid

Abbreviations

48.1 Abbreviations

6-APA	6-aminopenicillanic acid
AA	amino acid
ABP	arterial blood pressure
AC	adrenal cortex
ACE	angiotensin-converting enzyme
ACh	acetylcholine
AChE	acetylcholinesterase
ADH	antidiuretic hormone (= vasopressin, AVP)
AH	adenohypophyseal
AP	action potential
ATP	adensosine triphosphate
AVP	vasopressin (= antidiuretic hormone, ADH)
BMI	Body mass index
BP	blood pressure
BP	boiling point
CAH	carbonic anhydrase
cAMP	cyclic adenosine monophosphate
CG	cardiac glycoside
cGMP	cyclic guanidine monophosphate
CHO	Chinese hamster ovary
CHT	specific choline transporter
CML	chronic myeloid leukemia
CNS	central nervous system
COMT	catechol O-methyl transferase
CRH	corticotropin-releasing hormone
DAG	diacylglycerol
DHF	dihydrofolic acid, dihydrofolate
DHT	dihydrotestosterone
DNA	deoxyribonucleic acid
DPTA	diethylenetriamino-pentaaceticacid
DRC	dose–response curves
ECL	enterochromaffin-like
EDRF	endothelium-derived relaxant factor
EEG	electroencephalogram
EFV	extracellular fluid volume
EMT	extraneuronal monoamine transporter
ER	endoplasmic reticulum
FSH	follicle-stimulating hormone
GABA	γ-aminobutyric acid
GDP	guanosine diphosphate
GnRH	gonadotropin-releasing hormone = gonadorelin
GRH	growth hormone-releasing hormone = somatorelin
GHRIH	growth hormone release-inhibiting hormone = somatostatin
GTP	guanosine triphosphate
HCG	human chorionic gonadotropin
HIT II	heparin-induced thrombocytopenia type II
HMG	human menopausal gonadotropin
i.m.	intramuscular(ly)
i.v.	intravenous(ly)
IFN	interferon
IFN-α	interferon alpha
IFN-β	interferon beta
IFN-γ	interferon gamma
IGF-1	insulin-like growth factor 1
IL	interleukins
IOP	intraocular pressure
IP3	inositol trisphosphate
ISA	intrinsic sympathomimetic activity
ISDN	isosorbide dinitrate
ISMN	5-isosorbide mononitrate
LH	luteinizing hormone
M	moles/liter, mol/L
MAC	minimal alveolar concentration
MAO	monoamine oxidase
MDMA	methylene dioxymeth amphetamine
mesna	sodium 2-mercaptoethane sulfonate
MHC	major histocompatibility complex
MI	myocardial infarction
mM	millimoles/liter, mmol/L
mmHg	millimeters of mercury
mRNA	messenger RNA
mTOR	mammalian target of rapamycin
MW	molecular weight
NAChR	nicotinic receptor
NE	norepinephrine
NET	norepinephrine transporter
NFAT	nuclear factor of activated T cells
NH	neurohypophyseal
NMDA	N-methyl-Dasparate
NSTEMI	non-STEMI (non-ST elevation MI)
NTG	nitroglycerin
NYHA	New York Heart Association
PABA	p-aminobenzoic acid
PAMBA	p-aminomethylbenzoic acid
PDE	phosphodiesterase
PF3	platelet factor 3
PL	phospholipid
PLC	phospholipase C
PPARα	peroxisome proliferator-activated receptor alpha
PPARγ	peroxisome proliferator-activated receptor gamma
PRIH	prolactin release-inhibiting hormone = dopamine
REM	rapid eye movement
rER	rough endoplasmic reticulum
RNA	ribonucleic acid
rt-PA	recombinant tissue plasminogen activator
RyR	ryanodine receptors
s.c.	subcutaneous(ly)
sER	smooth endoplasmic reticulum
SERM	selective estrogen receptor modulators
SJS	Steven–Johnson syndrome
TEN	toxic epidermal necrolysis
SR	sarcoplasmic reticulum
SSRI	selective serotonin reuptake inhibitors
STEMI	ST elevation MI
THF	tetrahydrofolic acid, tetrahydrofolate
TIVA	total intravenous anesthesia
TMPT	thiopurine methyltransferase
TNFα	necrosis factor α
t-PA	tissue plasminogen activator

TRH	thyrotropin-releasing hormone = protirelin
VAChT	vesicular ACh transporter
VMAT	vesicular monoamine transporter

Pharmacodynamic parameters

B	specific binding of a ligand to a (receptor) protein
B_{max}	maximal specific binding of a ligand, indicating total density (concentration) of receptors in a sample
EC_{50}	concentration of an agonist that produces 50% of the maximal possible effect of that agonist
K_d	equilibrium dissociation constant of a ligand

Pharmacokinetic parameters

C	concentration of a drug in plasma
C_{max}	maximum plasma or serum concentration of a drug
C_0	initial concentration of a drug in plasma after i.v. injection
CL_{tot}	total clearance, i.e. volume of plasma cleared of the drug per unit of time
F	absolute biovailability, i.e. systemically available fraction of a drug in %
K_e	elimination rate constant from the central compartment
t½	elimination half-life, i.e. time required for the plasma concentration of a drug to reach half of its original value
t_{max}	time to reach the maximal plasma concentration (C_{max})
V_d	volume of distribution

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